Chapter 8: Kidney Disease in Elderly Diabetic Patients

Mark E. Williams and Robert C. Stanton

Renal Section, Joslin Diabetes Center, Boston, Massachusetts

Diabetes is a major health issue affecting the aging US population: epidemiologic studies show an increased prevalence of diabetes with aging. The reported incidence of diabetes in the elderly US population is at least 10 to 17%, caused by factors such as obesity, decreased activity, insulin resistance, and increased oxidative tissue damage. The prevalence of metabolic syndrome also increases with age and is frequently complicated by hypertension and chronic kidney disease (CKD). With further advances in the treatment of diabetes, longer lifespan is leading to more diabetes-related complications. Kidney disease secondary to diabetes has an increased prevalence in the geriatric population,[1] which comprises the fastest-growing subgroup of CKD and end-stage kidney disease (ESKD) in the United States. About one third of older diabetic individuals have microalbuminuria,[2] and an equal fraction have depressed kidney function. However, CKD care of the elderly diabetic patient remains underemphasized, and nephrology consultation remains underused. Clinical guidelines for type 2 diabetes in the elderly do not address CKD, and guidelines for diabetic CKD have not distinguished age groups.[3]

KIDNEY FUNCTION IN THE ELDERLY DIABETIC PATIENT

Renal blood flow and GFR diminish over time in elderly persons, minimized by a rise in the filtration fraction.[4] In older diabetic patients, the decrease in kidney mass, particularly from the renal cortex, and the histologic changes of diabetic nephropathy are compounded by advanced vascular changes.[5] The term "concealed renal failure" has been applied to elderly patients with normal serum creatinine but decreasing GFR.[6,7] The Modification of Diet in Renal Disease (MDRD) is increasingly used in the United States and has been found to be accurate in diabetic kidney disease.[8] A recent study of 160 diabetic patients reported that the MDRD equation has better accuracy than the Cockroft formula in moderate and severe kidney function.[9] Pathologically, the aging kidney may be associated with changes of basement membrane thickening and mesangial expansion that are also key histologic features of diabetic glomerulopathy.[1] Global glomerulosclerosis affecting the kidneys of elderly persons may relate to hyperperfusion, also observed in diabetes. However, studies of the diagnosis and prevalence of diabetic kidney disease in the elderly are lacking. Thus, there could be a higher prevalence of unusual presentations of diabetic kidney disease (*e.g.,* decreased GFR without albuminuria).[10] Nondiabetic glomerular syndromes present more commonly in geriatric patients because of conditions such as vasculitis, amyloidosis, paraproteinemia, membranous glomerulopathy, and antiglomerular basement membrane (GBM) disease. Another factor that needs to be considered in elderly persons is the existence of renal artery stenosis caused by atherosclerotic disease.

TREATMENT

The standard therapy of diabetic kidney disease is the triad of blood glucose control, BP control, and administration of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The goals that have been established through many clinical studies are a hemoglobin A1c of $<7\%$, a BP of $<130/80$ (with weak data supporting a lower systolic goal if proteinuria persists), and reduction of total urine protein to <500 mg/g of creatinine or of urine albumin to <300 mg/g of creatinine. Although these goals have been vali-

Correspondence: Mark Williams, Renal Section, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215. Phone: 617-732-2477; E-mail: mark.williams@joslin.harvard.edu

dated in a young to middle-aged population, they have not been tested in the elderly diabetic population.

Management of blood glucose level has been shown to be of major importance in patients with type 1 and type 2 diabetes mellitus in the prevention of complications. Recently the ADVANCE study[11] showed that tight control of blood glucose (glycated hemoglobin of 6.5 *versus* 7.3%) led to a 21% reduction in the incidence of diabetic nephropathy over a 5-yr period. The average age of the participants of this study was 66 yr old. In addition, an update to the UKPDS study on type 2 diabetic patients was recently published[12] and showed that, although there was a loss of difference in the glycated hemoglobin between the conventional and intensive treatment group over time, there were still significant benefits in cardiovascular outcomes and death rates for the original intensive treated group. Taken together, these results showed that tight glucose control in diabetic patients is important in preserving kidney function in an age range (54 to 73 yr) that will be relevant to the geriatric population.

BP control may be the most important factor in slowing progression of renal disease. For example, the Systolic Hypertension in the Elderly Program evaluated the effects of systolic hypertension, the most common pattern in elderly patients. A cohort of 2181 patients who were in the placebo arm of the study was examined to see the relationship between BP and decline in kidney function.[13] In general, the systolic BP ranged from 160 to 200 and the diastolic BP from 70 to 90 mmHg. The results showed that systolic hypertension (and not diastolic hypertension) strongly correlated with declining renal function. Because diabetic elderly patients are clearly at higher risk for significant decreases in BP, physicians caring for patients with diabetic kidney disease need to be aware of these to prescribe drugs appropriately and to determine how low to push the BP. Of note, a recently published follow-up of the UKPDS study on effects of BP on any diabetes-related outcome was not maintained unless the decrease in BP was maintained chronically.[14]

Third is the use of ACEIs and ARBs in diabetic elderly patients. These drugs slow progression of diabetic kidney disease in both type 1 and type 2[15,16] diabetic patients. The acknowledged current standard of care is to start an ACE-I or ARB in any patient with microalbuminuria or overt proteinuria. However, a recent study showed that many elderly patients are not being prescribed ACEI or ARBs,[17] presumably because of concerns over lack of benefit or untoward effects of ACE inhibitors and ARBs such as hyperkalemia and decreased GFR. No study has focused exclusively on the role of ACEI/ARBs in elderly persons, but considering their utility in other studies, some of which included elderly patients, it is reasonable to prescribe them at this time pending further studies. Both ACE inhibitors and ARBs will decrease GFR modestly, particularly initially. In general, if the drop is $<30\%$ and the GFR subsequently remains stable, therapeutic benefit is achieved. To monitor significant changes in potassium or GFR, it is routine to check potassium and serum creatinine 1 wk after starting or changing these medicines.

A principal outcome goal of these interventions is reduction of proteinuria.[18–20] A recent study explored the association of microalbuminuria in patients with and without hypertension and diabetes in a group that was 65 yr of age and older.[21] The results showed that there was a close correlation of microalbuminuria and cardiovascular disease, inflammatory markers (such as C-reactive protein), and systolic BP with increasing age. A variety of other factors including anemia affects the care of the elderly patient with diabetic nephropathy.[22] There is a danger of polypharmacy or confusion in the proper intake of prescribed medications. There may be significant cost limitations for elderly patients because of fixed income or rules of healthcare insurance coverage. As with ACEI/ARBs, there is an increased concern for side effects of medications. Thus, all of these factors should be taken into account when deciding on a particular treatment regimen. Unfortunately, epidemiologic studies suggest that elderly patients with CKD are not being referred for specialty care. In a report of mostly male patients with an average age of 66 yr, CKD, and diabetes over a 3-yr period from 2000 to 2002,[23] the authors estimated GFR using the MDRD formula. In the nearly 10,000 patients evaluated, almost one half of the patients had CKD. Of these, only 7.2% were referred to a nephrologist for care.

END-STAGE KIDNEY DISEASE

Although the number of elderly adults with diabetes has increased dramatically over the past two decades, it is far surpassed by their increase in ESKD, because of several factors including the willingness of providers to proceed with renal replacement therapy. A recent observational study of the US Renal Data System, for example, reported on octogenarians (78,419) and nonagenarians (5577) initiating dialysis between 1996 and 2003.[24] There was an average annual increase of about 10% in dialysis initiation in these very elderly patients. The most recent USRDS report indicates that incident rates of patients reported with diabetic ESKD and >75 yr old almost doubled between 1996 and 2006, the most recent year with data available, and prevalence rates have more than doubled.[25]

Little attention has been paid to this population in existing guidelines. In elderly persons, mortality rates worsen with kidney disease more than in other groups. In the general US population, persons 75 to 79 yr of age have an expected remaining life duration of 10.4 yr; for the elderly patient with ESKD, it is 2.6 yr,[26] and in the presence of diabetes, at least 25% less. Unique challenges include the high number of comorbid conditions, including ischemic coronary disease, congestive heart failure, and peripheral vascular disease. Cardiovascular disease develops in $>90\%$ of elderly diabetic patients before starting dialysis. Cognitive and psychiatric disorders, malnutrition, poor compliance, postdialysis hypotension, and dialysis access failure are common problems. ADA and other clinical practice guideline recommendations acknowledge differences in the

risks and benefits of glycemic control among individuals. Because uncontrolled hyperglycemia produces fluid overload or other problems such as decreased cognition, nocturia, incontinence, and impaired cognition, treatment is indicated. However, geriatric patients with ESKD may be less likely to benefit from long-term glycemic control in general and more likely to suffer from hypoglycemia. The elderly patient is at higher risk for drug-associated hypoglycemia. Nonetheless, monitoring glycemic control in diabetic ESKD remains far below recommended levels for hemoglobin A1c testing and prescription of diabetic test strips.[27]

Annual ESKD mortality risk in the elderly population is almost 50% and is higher for very elderly persons. Survival data for elderly diabetic patients are seldom reported separately.[24] Regarding choice of dialysis modality, one clinical study of USRDS patients from 1987 to 1989 comparing the mortality with treatment assignment (hemodialysis or peritoneal dialysis) suggested that the higher mortality risk with peritoneal dialysis (PD) patients was accentuated in diabetic and older patients.[28] Diabetic ESKD is the highest risk group for cardiac death. Diabetes and ESKD are both precursors to accelerated vascular calcification, involving coronary arteries, and are associated with poorer outcomes from percutaneous coronary interventions and coronary bypass surgery. Elderly diabetic patients with ESKD will also be at high risk for operative management of left main or multivessel disease, in which case medical therapy might be preferred. ESKD costs for diabetic patients exceed those for nondiabetic patients by 15 to 30%.[25]

TRANSPLANTATION

At a time when the maximum age of kidney patients considered for transplantation continues to increase, the growing numbers of elderly diabetic patients with CKD/ESKD raises significant questions regarding the appropriateness of kidney transplantation. The number of elderly patients on waiting lists for kidney transplantation began to increase in the 1990s, and transplant outcomes in elderly patients improved over a 15-yr period.[29] Concerns about limited life expectancy, high comorbidity rates, and relative organ shortages persist. The proportion of transplanted patients with diabetes is much lower (23%) than the percent of patients on dialysis who have diabetes. Both elderly patients and those with diabetic ESKD are more likely to be considered for expanded kidney donor lists. Older recipients are more likely to die with a functioning graft, decreased initial function, and delayed graft function.[30] A retrospective analysis of 5667 kidney transplant candidates $\geq$70 yr old using the Scientific Registry of Transplant Recipients database was recently reported.[31] Between 1990 and 2004, 2078 received a deceased donor kidney transplant and 360 received a living donor transplant. Mortality risk for those transplanted were compared with candidates remaining on the transplant list. Findings of 41% lower long-term mortality risk and better survival in elderly patients transplanted compared with those on the waiting list were especially true for elderly diabetic patients (53% reduction).

TAKE HOME POINTS

- Diabetes is the most common etiology of CKD/ESKD in the elderly
- Therapeutic trials of diabetic CKD/ESKD in elderly patients and guideline recommendations are insufficient
- Optimal management of diabetic CKD/ESKD in elderly patients may involve heightened risks and must take into account their increased mortality rates
- Increased number of elderly patients are being managed with dialysis, and some may benefit from a kidney transplant compared with remaining on dialysis

DISCLOSURES

None.

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REVIEW QUESTIONS: KIDNEY DISEASE IN ELDERLY DIABETIC PATIENTS

1. The number of elderly diabetic patients with CKD/ESKD is increasing because of all of the below EXCEPT
   a. Increasing rates of metabolic syndrome patients
   b. Higher referral rates for specialty care
   c. The overall risk of CKD increased with age
   d. Age-related loss of kidney function

2. Evaluation of the elderly diabetic patient with kidney disease must take into consideration all EXCEPT
   a. Histologic changes of diabetic glomerulopathy and aging
   b. Progression may occur independent of albuminuria
   c. Increase in nondiabetic glomerular syndromes
   d. Increased incidence of renovascular disease
   e. Reliance on validated measure of eGFR in the MDRD equation

3. Data regarding therapy for diabetic CKD indicate that
   a. Tight glycemic control is valuable and carries minimal risk
   b. Mild initial loss of GFR does not require cessation of ACEI therapy
   c. Diastolic BP control is more important than systolic control
   d. ACEI/ARBs are overused in this population
   e. There should be minimal concern about medication side effects