Diabetic Kidney Disease in Elderly Individuals

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KEYWORDS

• Diabetes • Kidney disease • Elderly individuals

KEY POINTS

- Elderly individuals represent the fastest growing subgroup of the US general population, and diabetes mellitus is now a major health issue affecting them.
- Chronic kidney disease complicates diabetes and also has an increased prevalence in elderly individuals.
- The kidneys are among the most prominent body organs affected by both the aging process and by diabetes.

INTRODUCTION

Elderly individuals represent the fastest growing subgroup of the US general population, and diabetes mellitus is now a major health issue affecting them. The reported incidence of diagnosed diabetes in this elderly cohort is 10% to 18%, compared with roughly 8% of the general population. In the decade between 1994 and 2004, the prevalence of diabetes in persons more than 65 in the United States increased by 62%.[1] A recent report documented that the prevalence of both diabetes and prediabetes have reached new levels,[2] with total crude prevalence (diagnosed and undiagnosed cases) reported as 30% for those older than 60 years. This growing epidemic has been linked to obesity, tobacco use, urbanization, physical inactivity, poor nutrition, and improved survival of diabetic patients, and aging.[3] The number of individuals globally with diabetes and older than 65 years, which doubled between 1900 and 2000, is projected to double again by 2030 (**Fig. 1**).[4]

Chronic kidney disease (CKD) complicates diabetes and also has an increased prevalence in elderly individuals. Particularly in those older than 60 years, the most common cause of CKD and end-stage renal disease (ESRD) in the United States is diabetic kidney disease.[5] A third of new ESRD cases in people older than 75 years are caused by diabetic nephropathy. According to prevalence estimates from the Third National Health and Nutrition Examination Survey (NHANES III), approximately a third of older diabetic individuals have microalbuminuria, the earliest clinical stage

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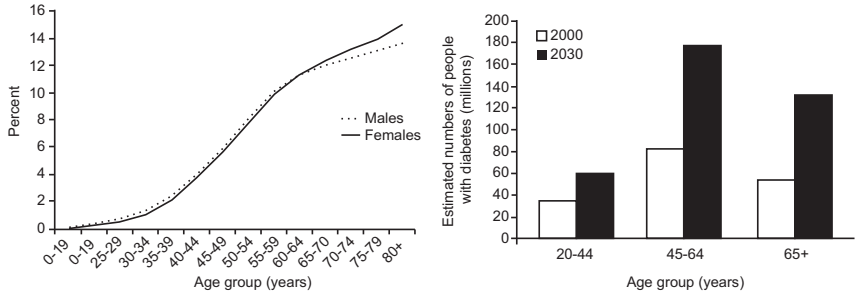

Fig. 1. Global diabetes prevalence by age and sex in 2000 (*left*), and estimated number of adults with diabetes by age group worldwide in 2000 and 2030 (*right*). (*Data from* Wild S, Roglic G, Gren A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047–53.)

of diabetic kidney disease (although a nonspecific finding). Among 2570 older patients with diabetes in the US Veterans' Integrated Service Network, nearly half (48%) were afflicted with CKD, most of the time mild to moderate in severity.[6] A recent report on the prevalence of CKD and comorbid illness in elderly persons determined from 3 sources: laboratory tests in the Kidney Early Evaluation Program (KEEP) (a free community-based health screening program that targets adults at high risk of kidney disease based on personal or family history), NHANES (the cross-sectional probability samples of the civilian noninstitutionalized US population), and the prevalence of diagnosed CKD determined from billing codes of a random 5% sample of the US Medicare population. In all 3 data sets, the prevalence of CKD was higher in individuals suffering with diabetes (KEEP 48% vs 40%, NHANES 58% vs 41%, Medicare 14% vs 4%).[7]

Over the past quarter century, the fraction of patients with diabetic renal disease in the total population initiating dialysis in the United States has increased from about one-sixth to almost half, related to the epidemic of diabetics and the increased acceptance of diabetic patients into dialysis programs. Patients with diabetes as the primary causes of kidney failure now account for 45% of the incident (ie, new) ESRD population annually, up to a third of patients with type 2 diabetes develop ESRD and require renal replacement therapy for survival.[8] Internationally, Malaysia, Mexico, and the United States have the highest percentage of incident patients with ESRD with diabetes. Diabetes is responsible for half of all ESRD cases in New Zealand and Singapore, and is the fastest growing cause of ESRD in Europe.[9] Diabetes was present in 37% of elderly patients with ESRD in Canada.[10] This growing population represents unique challenges in multidisciplinary medical management. Many carry multiple comorbid conditions, such as ischemic heart disease, congestive heart failure, and peripheral vascular disease. Patients have hearing and visual disabilities, coexisting cognitive[11] and psychiatric disorders, frequently require nursing home care or assisted living, and may be unwilling or unable to comply with their proposed treatment. Diabetic ESRD is also associated with increased risk of dementia, especially as a result of vascular disease, leading to adverse outcomes. Both elderly and diabetic patients are less likely to have an arteriovenous fistula, the dialysis access recommended to cause fewer complications.[12]

PATHOPHYSIOLOGY

The kidneys are among the most prominent body organs affected by both the aging process and by diabetes. Kidney function and morphology are known to change with

age. The kidney biopsy of a healthy elderly individual may include pathologic findings that have been considered a nonspecific part of the normal aging process.[13] Common findings in kidney biopsies of elderly individuals, variable in severity, include advanced vascular changes, fibrosis related to collagen accumulation and global sclerosis.[14] increases in mesangial and endothelial cell numbers, and relative podocyte depletion. Age-related increase in kidney fibrosis has been related to increased collagen accumulation.[15]

Pathologically, the aging kidney may be associated with mesangial matrix expansion and basement membrane thickening, nonspecific findings that are also recognized as key features of diabetic glomerulopathy. The contribution made by the aging process itself to age-associated CKD carries the potential that it could be accelerated by superimposed conditions such as diabetes.[16] In older diabetic patients, classic findings of diabetic glomerulopathy (mesangial expansion, glomerular basement membrane thickening, Kimmelstiel-Wilson nodules) are compounded by advanced vascular changes,[17] which may be accompanied by adaptations that produce glomerular hyperperfusion injury. As an age-associated disease, it has been proposed that diabetes may accelerate cell and organ senescence in humans. It has recently been proposed that age-associated glomerulopathy may be understood as a senescence process affecting kidney cells such as the podocyte and accelerated by superimposed conditions such as diabetes, so that age-related changes are aggravated by diabetes. In the diabetic kidney, these changes would hinder the already limited ability of aged kidney tissue to repair itself. Verzola reported that diabetic nephropathy is associated with an acceleration of a senescent phenotype in kidney cells, using assays for senescence markers in kidney biopsies of patients with type 2 diabetic nephropathy.[18] The investigators propose that hyperglycemia may trigger the loss of repair capabilities, promote the early occurrence of senescence, and contribute to nephron loss in diabetic kidney disease. Hyperglycemia may also trigger oxidant stress and make it more difficult for kidney cells to undergo repair, leading to a state of accelerated senescence. A recent study by Tsaih and colleagues[19] suggested a common pathway for diabetic-related and age-related renal disease by finding genetic overlap of loci associated with albuminuria in aging mice and with proteinuria in human diabetic patients. Using a haplotype-association mapping approach was used to identify quantitative trait locus linkage. One significant and 8 suggestive loci were found. These loci were then compared with genome-wide association scans for diabetic nephropathy from a previously reported genome-wide association study.[20] Two of the 9 mouse loci for age-associated albuminuria were significantly associated with diabetic nephropathy.

Pathologic changes of aging may also reflect accumulation of advanced glycation end products (AGEs) in kidney tissues in aging and diabetes. Increasing evidence indicates that AGEs do accumulate during normal aging and contribute to the aging phenotype.[21,22] Glycation is a slow, nonenzymatic reaction between free amino groups in proteins and reducing sugars such as glucose that leads to the formation of heterogeneous end products. The expression for receptor for AGE (RAGE), an important transducer of AGE effects, is increased in both aging and diabetes. AGEs accumulate at an accelerated rate during the course of diabetes[22] and have been implicated in diabetic complications. AGEs are believed to be important contributors to inflammation in aging.[23] AGEs promote oxidation and inflammation through cell surface RAGE receptors. It has been recently proposed by Vlassara and colleagues[24] that the decline in kidney function with aging may be linked to oxidative stress and inflammation. In aging mice, greater oxidant intake is associated with increased age-related CKD.[25] Diabetic patients also have high serum AGE levels and increased oxidative stress and inflammation in the diabetic kidney. The role of AGE deposition in elderly humans with diabetic kidney disease remains to be determined.

Natural History

The classic presentation of CKD caused by diabetes mellitus is albuminuria initially, followed later by a decline in glomerular filtration rate (GFR). The typical course of diabetic nephropathy from microalbuminuria to CKD to ESRD is shown in **Fig. 2**.[26] However, compared with the classic presentation for diabetic nephropathy in younger individuals (heightened function then albuminuria followed by loss of function), it is known that there may be a higher prevalence of atypical presentations of diabetic kidney disease in this population (for example, decreased GFR without albuminuria). In 1 study, two-thirds of elderly diabetic patients with age-adjusted kidney impairment were lacking albuminuria.[27] Conversely, the presence of albuminuria in the elderly diabetic patient is often caused by conditions other than diabetic kidney disease.

Accurate assessment of kidney function is required for determining the prevalence and natural progression of kidney impairment, for morbidity and mortality risk stratification associated with CKD, and for evaluating the impact of new therapies in elderly populations. Moderate reductions in kidney function with aging have been shown both in cross-sectional and longitudinal surveys such as NHANES, and also in a series of healthy potential kidney donors.[28] The decline is associated with a proportionate decrease in renal blood flow. According to cross-sectional and longitudinal studies, GFR decreases by about 1 mL/min/1.73 m^2 after about age 30 years as a result of physiologic aging[29] (without diabetes). The age-related decline in kidney function seems to continue after age 60 years, so that normal GFR when measured as inulin clearance is about 80 mL/min/1.73 m^2 for those aged 75 to 79 years, and 65 mL/min/1.73 m^2 for those 80 to 89 years of age. Nonetheless, as a result of the typical age-related loss of function, elderly patients may be mislabeled as having moderate CKD despite the fact

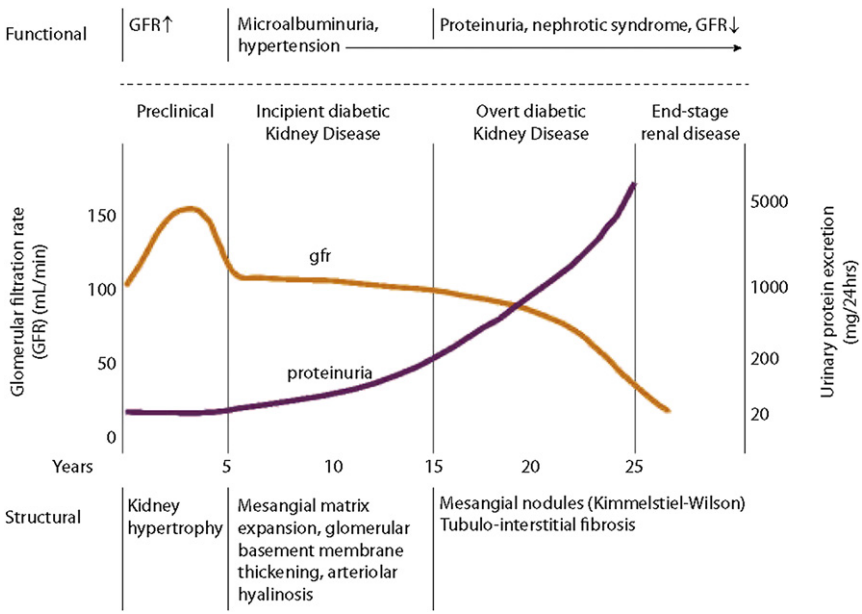

Fig. 2. Natural history of diabetic nephropathy, including functional and structural manifestations (course typical of type 1 diabetes). (*From* Vora JP, Chattington PD, Ibrahin H. Clinical manifestations and natural history of diabetic nephropathy. In: Comprehensive clinical nephrology. Elsevier; 2000; with permission.)

that their GFR corrected for age is not reduced.[30] Although most individuals have a decline in kidney function after age 30 years, up to a third did not in a recent longitudinal study. The natural history of the disease must be interpreted with this reality in mind, and the additional effect of disease progress on kidney function should be age-adjusted.[31]

Glomerular hyperfiltration is a well-characterized feature of type 1 diabetes that may be regarded as a potential risk factor for nephropathy complications in those patients. Age-unadjusted definitions of hyperfiltration range from 125 to 140 mL/min/1.73 m^2. In a survey of 662 patients with type 2 diabetes, GFR was measured by 99-tech-DTPA, and hyperfiltration determined using an age-unadjusted threshold of more than 130 mL/min/1.73 m^2 and incorporating a decline of 1 mL/min/1.73 m^2/y after age 40 years (**Fig. 3**).[32] The prevalence of hyperfiltration was 7.4% with age-unadjusted and 16.6% with age-adjusted definitions. In those older than 65 years, adjusting for age increased the prevalence of hyperfiltration from 0.3% to 9.0%. Its pathogenic significance continues to be explored.

The natural history of elderly diabetic patients with CKD is also dominated by the cardiovascular complications of diabetes and diabetic kidney disease. Substantial observational evidence indicates that albuminuria is associated with increased risk of cardiovascular disease.[33] In a recent report of patients older than 65 years with and without hypertension and diabetes, a close correlation was found between microalbuminuria and cardiovascular disease, inflammatory markers such as C-reactive protein, and systolic blood pressure.[34] Other factors may be a long history of hypertension, preexisting kidney disease, exposure to nephrotoxic medications, and renal ischemia caused by atherosclerotic occlusive disease.

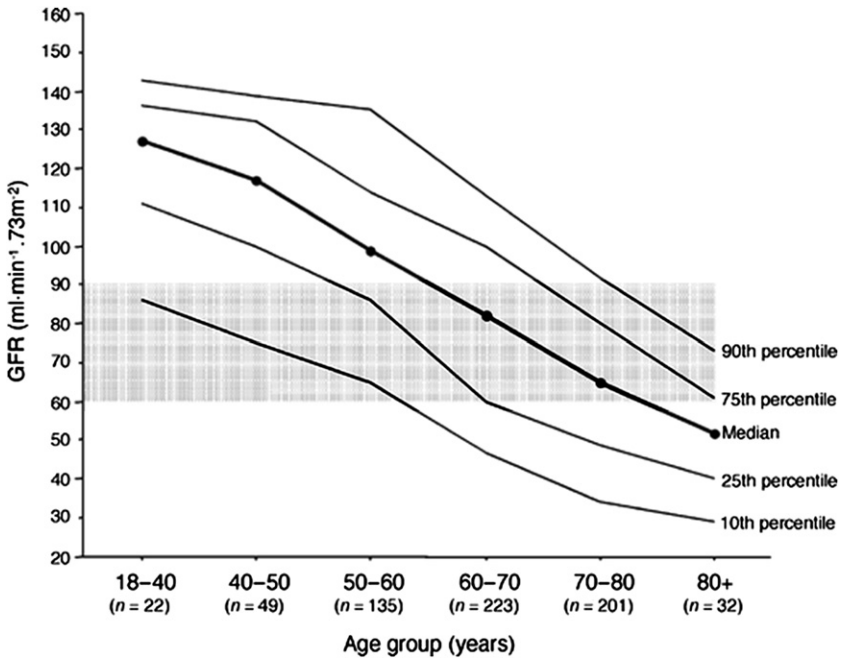

Fig. 3. Age-related decline in kidney function in patients with type 2 diabetes. (*From* Premaratne E, MacIsaac RJ, Tsalamandris C, et al. Renal hyperfiltration in type 2 diabetes: effect of age-related decline in glomerular filtration rate. Diabetologia 2005;48:2486–93; with permission.)

Diagnosis

There are few studies on which to base a diagnostic approach to diabetic kidney disease in elderly individuals. For example, how often diabetic retinopathy is absent, what the proper duration of diabetes is, and how commonly microscopic hematuria is present, are not clear. Screening for diabetic complications such as nephropathy should therefore be individualized in older adults. Evaluation of the elderly diabetic patient with kidney disease must take into account the different and frequently overlapping histologic changes of diabetic glomerulopathy and aging, the increase in nondiabetic glomerular diseases, progression occurring independent of albuminuria, and an increased incidence of renovascular disease; a second factor is the likelihood that loss of function may be instead caused by aging itself. There could be a higher prevalence of unusual presentations of diabetic kidney disease in the elderly patients (for example, decreased GFR without albuminuria), although there are no studies that have addressed this issue. Another factor that needs to be considered in elderly individuals is the existence of renal artery stenosis related primarily to atherosclerotic disease (renin-angiotensin-aldosterone system [RAS]). Indications for a kidney biopsy should include an active urinary sediment (many red blood cells or white blood cells or casts), high quantity of proteinuria (especially greater than 3 g/24 h), or a rapidly declining estimated GFR (eGFR).

TREATMENT

The standards of therapy for diabetic nephropathy in the general population are the triad of blood glucose control, blood pressure control, and administration of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). The goals that have been established through clinical studies are a hemoglobin A1c (HbA1c) of less than 7%, a blood pressure of less than 130/80, and reduction of total urine protein to less than 500 mg/g of creatinine, or of urine albumin to less than 300 mg/g of creatinine. These goals have been validated in a young to middle-aged population, but not in the elderly population. As a result, although CKD care of the elderly diabetic patient is central to their management, guidelines in the United States as well as Europe only marginally address this difficult population.[35]

To what extent should issues of CKD treatment and outcomes be addressed differently in the geriatric diabetic population? Significant drawbacks in their application to the elderly diabetic population do exist: (1) the goals have been validated in young to middle-aged diabetic kidney patients and they do not distinguish between different age groups. Neither the efficacy nor safety of these goals may take into account the special needs of elderly patients with diabetes. For example, the risks of tight glycemic control have emerged in several recent studies of the general diabetic population.[36–39] (2) The guideline-based approach emphasizes primary and secondary prevention of diabetic kidney disease as a microvascular complication, although the elderly diabetic population may have more advanced microvascular disease, mixed renal pathophysiology, and advanced macrovascular disease; and (3) data are not available to prioritize the recommended interventions, a problem of greater relevance to the elderly population. Elderly diabetic patients with CKD may have different needs emanating from their greater frailty, higher comorbidity index, and shorter life expectancy, and may warrant a lower renoprotection treatment intensity than a younger population.[40] As noted in a recent review by Abatteruso and colleagues,[41] neither the EDAC (European Diabetes and Aging Guidelines), the ADAG (American Diabetes and Aging Guidelines), the National Kidney Foundation Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for

Diabetes and CKD, nor the Quality Indicators for the Care of Vulnerable Elders 3 (ACOVE-3) adequately address diabetic CKD in elderly individuals. For example, a time horizon (time to expected benefit) of glycemic management could exceed that of RAS blockade or hypertension control and must be measured against life expectancy in elderly individuals. Glycemic control may take as long as 8 years to positively affect microvascular complications.[40]

Nonetheless, evidence that benefit of treatment is occurring has emerged from a recent analysis from the Centers for Disease Control and Prevention, which determined that the decline in diabetes-related ESRD incidence included all age groups, including those older than 75 years (**Fig. 4**).[42] Using US Renal Data System data, Burrows and colleagues analyzed patients with incident ESRD who had diabetes listed as their primary diagnosis between 1990 and 2006. Incidence was calculated using the estimated US population with diabetes from the National Health Survey, followed by age adjustment. Whereas the number of those with diabetes-related ESRD treatment almost tripled between 1990 and 2006, the age-adjusted diabetes-related ESRD incidence decreased from 1996 to 2006, by 3.9% per year. Among individuals aged 65 to 74 years, rates decreased by 3.4% (beginning in 1998), and for those 75 years or older, by 2.1% (beginning in 1999). (Previously reported data had shown declining incidence only for those younger than 65 years.)

Glycemic Control

A recent report on the management of diabetes in elderly patients complicated by CKD[40] reviewed recent guidelines and data limitations on the matter. Regarding glycemic control, the KDOQI 2005 guidelines on diabetes and CKD emphasized the benefit of strict metabolic control early in progression, (ie, prevention of microalbuminuria), with evidence weak in later stages.[43] Although improved glycemic control may significantly reduce the risk of microvascular complications, the benefit on cardiovascular outcomes remains uncertain. No studies have prospectively evaluated the impact of intense glycemic control in patients older than 65 years. The UKPDS (United Kingdom Prospective Diabetes Study) is usually cited as the major large randomized

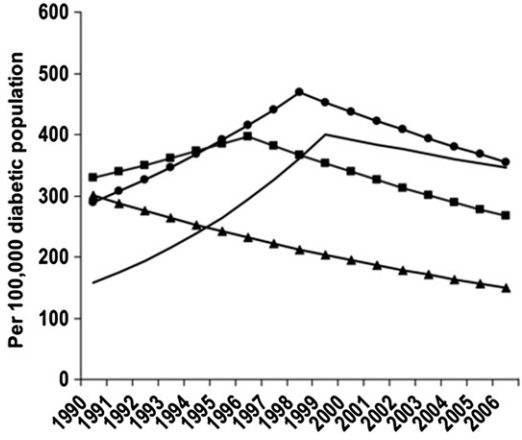

Fig. 4. Age-specific incidence of diabetes-related ESRD in the US population with diabetes mellitus, from 1990 to 2006. Symbols: triangles, <45 years; squares, 45–64 years; circles, 65–74 years; line, ≥75 years. (*From* Burrows NR, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continue to decline. Diabetes Care 2010;33:73–7; with permission.)

controlled study in type 2 diabetes (patients 53.4 ± 8 years) to confirm the benefit of glycemic control in reducing microvascular complications.[44]

On the other hand, the risks of tight glycemic control in the general diabetes population have emerged in several recent studies. Collectively, 3 large trials (ACCORD [Action to Control Cardiovascular Risk in Diabetes], mean age 62 years[45]; ADVANCE, mean age 66 years[46]; and VADT, mean age 60 years[47]) have evaluated nearly 23,000 individuals with type 2 diabetes. Renal benefit varied among the studies, whereas cardiovascular benefit was lacking in all 3 trials. In ADVANCE, for example, the renal benefit involved a 21% reduction in the incidence of kidney disease (albuminuria) in the intensive treatment group. Importantly, hypoglycemia affected a significant proportion of patients in the intensive treatment groups of all 3 studies. The ACCORD study compared a strategy of intensive control (HbA1c target <6.0%) or standard control (hemoglobin target 7%–7.9%). The targeting of normal glycemic levels for 3.5 years led to increased mortality and did not significantly reduce major cardiovascular events or renal outcomes. In the ADVANCE study, severe hypoglycemia occurred occasionally but more commonly in the intensive control group. Intensification of therapy in older patients should be approached cautiously.

Definitive studies on the effects of glycemic control on progression of kidney disease in elderly individuals are lacking. Hyperglycemia leading to symptoms or risk of acute hyperglycemia complications should be avoided in all patients, including elderly patients. Recent guidelines regarding older patients with diabetes now recommend individualized care based on comorbid conditions, projected life expectancy, health care goals, and treatment preferences.[48] Only adults who are functional and have significant life expectancy should have the same diabetes treatment goals as younger adults.[49] The presence of advanced CKD further complicates management and requires prudence because of increasing comorbidities, limited life expectancy, and effects of kidney impairment on drug metabolism. Oral hypoglycemic agents to be avoided include chlorpropamide and glyburide (severe hypoglycemia) and metformin (fatal lactic acidosis).[50]

Blood Pressure Control

Hypertension is a hallmark of diabetic CKD in general, and in elderly patients may be present before kidney disease becomes evident. Central mechanisms are believed to involve the additive consequences of increased extracellular volume and enhanced vascular tone. Hypertension management of the elderly diabetic kidney patient suffers many of the same uncertainties as does glycemic control, although benefits to be derived from blood pressure control could occur significantly earlier. Hypertension is associated with worsening kidney function in diabetes, as well as cardiovascular complications such as stroke, major cardiovascular events, and heart failure. The importance of blood pressure control in slowing progression of diabetic kidney disease in younger individuals has been established in many studies.

The threshold for high blood pressure treatment is generally defined as 140/80 for elderly type 2 diabetic patients, whereas the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*[51] defines hypertension as greater than 130/80 in the setting of diabetes or CKD. High blood pressure is presents in 40% to more than 90% of diabetic patients suffering from kidney complications. Its prevalence increases as kidney disease progresses, from microalbuminuria to kidney impairment. In addition, systolic pressure tends to increase, whereas diastolic blood pressure decreases after 66 to 69 years. Isolated systolic hypertension is the most common hypertension pattern in the elderly population. Furthermore, data from the Systolic Hypertension in the Elderly Population

study, which included a small percentage of diabetic patients, showed a stronger correlation of systolic pressure with declining kidney function.[52] Over the full range of systolic pressures, the risk of kidney disease progression increased 2-fold.

Although several hypertension guidelines published in recent years have included management of hypertensive diabetic patients, specific recommendations for the elderly subgroup are lacking. Many studies that provide evidence for the guidelines have had limited sample sizes of diabetic patients, particularly those older than 70 years. Evidence for basing medical conclusions for the benefit/risk of tight blood pressure control on CKD progression in elderly diabetic patients is inadequate. Controlling blood pressure may be more important for prevention of cardiovascular risks, with potential benefits to reduce the risk of cardiac and neurologic events. Because of this situation, cardiovascular risk assessment should be completed at the time of diagnosis of hypertension. There are no randomized clinical trials to establish target blood pressures for elderly diabetic patients with CKD, so that uncertainty persists. For frail elderly patients, a goal of 150/80 may be acceptable. Likewise, there is no specific mix of blood pressure medications that is better in elderly patients compared with other groups. However, the selection of antihypertensive agents that provide renoprotection, such as RAS blockers, are recommended as first-line agents. Guidelines in general support the use of renin-angiotensin blockade and diuretics as initial therapy.[53] For cardiovascular risk, ACEI are viewed as the most beneficial agents. For hypertension control, more than 1 agent is typically necessary.

There remains debate as to how low the blood pressure should be decreased. The debate centers in part around uncertainty as to whether there is a J-shaped curve in mortality (ie, whether there could be an increase in mortality and worsening of kidney disease when blood pressure decreases less than a certain level). Diabetic elderly patients are clearly at higher risk for significant decreases in blood pressure for several reasons. Elderly patients tend to have decreased intake of salt and water, and may have higher losses of salt and water through perspiration and urine/stool losses. In addition, elderly individuals, and especially diabetic elderly patients, tend to have some degree of autonomic dysfunction. This situation prevents an increase in both heart rate and vasoconstriction with upright posture, leading to postural hypotension. Further risks of excessive decrease of blood pressure may occur with antihypertensive agents, so that physicians managing patients with diabetic kidney disease need to be aware of such risks, in order to prescribe drugs appropriately and to determine the age-appropriate blood pressure goal. In general, it seems that less than 140/90 mm Hg is a reasonable target.

RAS Blockade

Another important therapeutic intervention is the use of ACEI and ARBs in diabetic elderly patients. The value of these drugs in slowing progression of diabetic kidney disease has been established for both type 1[54] and type 2[55,56] diabetic patients. The acknowledged current standard of care is to start an ACEI or ARB in any patient with microalbuminuria or overt proteinuria even if blood pressure is at goal. Based on pathophysiologic evidence that overactivity of RAS is a dominant factor in the disease, clinical trials have led to the use of ACEI and ARBs as standard agents for diabetic kidney disease since the late 1990s. RAS activation is now known to lead to hemodynamic, biochemical, and histologic effects in diabetic glomerulopathy. RAS blockade improves systemic and intrarenal hemodynamics and the glomerular filtration barrier, and reduces intraglomerular pressures.

Current practice guidelines promulgated by the American Diabetes Association, the Joint National Commission, and the National Kidney Foundation support the use of

both ACEI and ARBs as initial therapies for diabetic kidney disease. Both ACEI and ARBs are more effective than other antihypertensives in reducing proteinuria[57] and slowing the progression to kidney failure in patients with diabetic CKD. Both agents have superior antiproteinuric effects compared with other agents. In this largely hypertensive population, RAS blockers are more advantageous than other agents when blood pressure remains more than goal and achieve less superiority when blood pressure has been normalized. One important caveat is that kidney function may initially decline, because angiotensin blockade effectively lowers systemic pressures. However, mild initial loss of glomerular filtration (25%) may reflect effective RAS blockade and need not require cessation of ACEI or ARB therapy. In addition to stabilization of kidney function, a principal outcome target of RAS blockers and an earlier sign of efficacy is reduction in proteinuria. Clinical trial data do indicate that worse proteinuria is associated with a greater likelihood of progressive loss of function in diabetic kidney disease.[58]

Nonetheless, direct evidence of the benefit of RAS blockers in elderly patients remains unproved, and their use is an extrapolation from adult clinical trials of mostly middle-aged patients. There have been no large-scale clinical trials using ACEI to prevent kidney failure in type 2 patients. In the primary trials using ARBs, the mean age of participants was about 60 years. Regulatory trials indicated that in patients who already have progressed to overt nephropathy and have impaired GFR, ARBs can slow the progression to ESRD, albeit not stopping or reversing the decline. RENAAL was a large-scale randomized placebo-controlled trial evaluating losartan 50 to 100 mg daily against placebo in 1513 type 2 patients who were followed for 3.4 years.[55] The benefit was significant, with assignment to the ARB arm reducing the risk of doubling of serum creatinine by 25% and of ESRD by 28%. Furthermore, proteinuria was reduced by 35%, and reduction in ESRD risk was proportional to the decrease in proteinuria achieved. In those who did have a doubling of serum creatinine, the later development of ESRD was still less likely with the study drug. Confirmation of the RAS blockade benefit for CKD occurred in the IDNT trial,[56] a second landmark RAS blockade trial, and for slowing of microalbuminuria in the IRMA trial.[59]

Of importance to geriatric kidney disease, a recent follow-up report evaluated the safety and efficacy of losartan in the roughly one-quarter of patients in the RENAAL study who were 65 years of age. The investigators tested for effect modification by age of the impact of losartan on the incidence of the predefined end points (doubling of serum creatinine, ESRD, or death). The incidence of adverse events was also analyzed. The older group had the same benefit as the younger participants, even with no more risk for worsening of creatinine or potassium levels. Losartan reduced the risk of a composite outcome of creatinine doubling, ESRD, and death in this group.[60] Furthermore, in the oldest tertile, the rate of doubling of baseline serum creatinine was reduced by 38% with losartan, and the event rate of ESRD by 50%. Although not specifically conducted in an elderly population, the study provides the best clinical trial evidence available in support of ARB blockade of the RAS in older patients. However, CKD in the elderly diabetic population may frequently lack proteinuria and therefore be less responsive to RAS blockade. In NHANES III, a third of those surveyed with type 2 diabetes aged 60 to 70 years and with normal urinary albumin excretion nonetheless had a GFR of less than 30 mL/min, and almost half were between 30 and 60 mL/min.[61] Many studies have shown that increases in protein in the urine increase the risk of progressing to renal failure.[58]

Many elderly diabetic patients are apparently not prescribed ACEI or ARBs. In a study of Medicare patients in 2002 in Pennsylvania,[57] most of whom were 75 to 84 years of age, only about half of the hypertensive kidney patients were on either

an ACEI or ARB. The investigators reviewed Medicare data for 2002 on patients residing in Pennsylvania who had diabetes. Of 30,750 patients identified, 21,053 had hypertension and 1243 were identified as having proteinuria or proteinuria and kidney disease. Most patients were 75 to 84 years old. Of the hypertensive only patients, 50.5% were on an ACEI or ARB; of the proteinuria patients, 40%; and for those with both hypertension and proteinuria, 54.7%. In each diagnostic category, roughly 25% fewer were under ACEI/ARB therapy than in a separate report regarding a younger cohort.[55] The investigators speculate that safety concerns about hyperkalemia and reduction in kidney function either acutely or during progression to ESRD, and lack of efficacy data in elderly individuals, underlie the prescription pattern. A recent study of a large community-based cohort in Canada also provided data on ACEI/ARB use.[62] The study evaluated the impact of estimated GFR reporting with nephrology visits and health care resource use. After the implementation of eGFR reporting, the rate of first outpatient nephrology visits for CKD increased by 68.4%, and referral rates were even higher for elderly patients with diabetes. Reporting of eGFR was not associated with an increase in ACEI/ARB use, perhaps because most (77.5%) of the elderly patients with diabetes were already under treatment.

Preventing cardiovascular morbidity and mortality may be a more important factor than delaying progression to ESRD, and may affect the selection of ACEI/ARBs in elderly patients. Existing guidelines suggest that when reducing cardiovascular risk is the priority, ACEI should be considered first-line therapy, and ARBs the first alternative. In addition, many studies have showed that microalbuminuria and proteinuria are strong risk factors for cardiovascular disease.[63–65] A recent study by Barzilay[34] explored the association of microalbuminuria in patients with and without hypertension and diabetes in a group that was 65 years and older. This investigator evaluated a wide range of variables, including endothelial dysfunction and inflammatory markers, in an effort to determine why there is a close association between microalbuminuria and cardiovascular disease. The results showed that there was a close correlation of microalbuminuria and cardiovascular disease with increasing age, inflammatory markers (such as C-reactive protein), and systolic blood pressure. These results underscore the importance of implementing blood pressure control and other approaches (blood glucose control and the use of ACE inhibitors and ARBs) in patients with microalbuminuria in order to reduce the risk of cardiovascular disease.

COMPREHENSIVE THERAPY

It should not be surprising, based on this information, that little is known about the risks/benefits of multiple combined therapies for diabetic CKD in elderly individuals. One study from Scotland by Joss and colleagues[66] of 90 patients whose mean age was 63 years (57% men and 43% women) showed the potential importance of aggressive intervention. The study was a prospective randomized controlled study. Patients with type 2 diabetes and nephropathy were randomly allocated to an intensive group ($n = 47$) or control group ($n = 43$) and followed for 2 years. Treatment targets were the same for both groups, but the intensive group were seen as often as required to meet the targets; controls were seen at their normal clinics. Specifically the treatment goals were: systolic blood pressure less than 140 mm Hg, diastolic blood pressure less than 80 mm Hg, HbA1c less than 8%, sodium intake less than 120 mmol/d, protein intake 0.7 to 1 g/kg of ideal body weight per day, and cholesterol less than 4 mmol/L or cholesterol/high-density lipoprotein cholesterol ratio less than 4. The primary end point was the rate of progression of renal disease in the second year. The results showed that the median rate of loss of kidney function (creatinine clearance) in the

intensive group decreased from 0.44 mL/min/mo in the first year to 0.14 mL/min/mo in the second year, compared with 0.49 mL/min/mo and 0.53 mL/min/mo in the control group ($P = .04$ for second year). In this study, the intensively treated group achieved a rate of decline similar to the nondiabetic, healthy population, which is 1 mL/min/y or 0.083 mL/min/mo. Considering that the mean creatinine clearance at the start of the trial was 55 mL/min, these results if sustainable could delay the onset of dialysis by several years in the intensive group compared with the control group.

For other treatment considerations of diabetic CKD, it is reasonable to assume that treatment approaches considered for younger patients may not apply to elderly individuals. These approaches include drugs already approved for hypertension (aldosterone blockers, renin inhibitors) or for other indications (vitamin D analogues, thiazoledinediones, statins). The risk/benefit ratios of existing therapies for diabetic CKD as applied to the elderly population remain largely undetermined. For emerging therapies, inclusion of elderly patients in regulatory trials, taking into account the GFR decline caused by aging, the prevalence of nondiabetic kidney disease, and the potential for excessive risk, is a desirable goal.

SUMMARY

The treatment of diabetic nephropathy in elderly individuals is based primarily on data from younger age groups. However, the assumption that the same treatment approaches for the younger age groups can be uniformly applied to elderly individuals is likely to be incorrect. The cornerstones of aggressive therapy for diabetic kidney disease in general may have drawbacks in elderly patients. For example, significant risks of tight glycemic control have emerged in recent studies. Excessive decrease of blood pressure to existing targets may be unsafe in elderly individuals. Limited data do indicate that renin-angiotensin blockade may be as effective and no riskier than in middle-aged diabetic kidney patients. Until further studies are carried out, it is prudent to treat the elderly patient with similar approaches as in younger patients, but tempered by the issues reviewed in this article. There is a growing need for the development of clinical guidelines to retool CKD management in the elderly diabetic population using both current and emerging therapies.

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