Clinical Challenges in Diagnosis and Management of Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is a major and increasing worldwide public health issue. There is a great need for implementing treatments that either prevent or significantly slow the progression of DKD. Although there have been significant improvements in management, the increasing numbers of patients with DKD illustrate that current management is not wholly adequate. The reasons for suboptimal management include the lack of early diagnosis, lack of aggressive interventions, and lack of understanding about which interventions are most successful. There are a number of challenges and controversies regarding the current management of patients with DKD. Understanding of these issues is needed in order to provide the best care to patients with DKD. This article describes some of the clinically important challenges associated with DKD: the current epidemiology and cost burden and the role of biopsy in the diagnosis of DKD. Treatment controversies regarding current pharmacologic and nonpharmacologic approaches are reviewed and recommendations based on the published literature are made.


INDEX WORDS: Diabetic kidney disease (DKD); diabetes mellitus; renal disease; prevalence; public health.

EXECUTIVE SUMMARY

Diabetic kidney disease (DKD) accounts for a large proportion of nephrology practice, and there is an overwhelming need to implement treatments that will either prevent the development or significantly slow the progression of DKD. Current approaches are not adequate because the number of patients who develop DKD or have progressive DKD continues to increase. Many controversies exist regarding standard approaches to patients with both diabetes and renal disease. This review discusses some of the clinically important challenges associated with the diagnosis and management of DKD.

Chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m² or urine albumin-creatinine ratio > 30 mg/g) is estimated to affect 13.1% of the US population. Diabetes is the most prevalent cause of end-stage kidney disease, followed by hypertension. The Centers for Disease Control and Prevention (CDC) estimate that 1 in 3 adults in the United States will have diabetes by 2050 if current trends continue, suggesting that there will be a very significant increase in DKD in the future. However, data for the prevalence of CKD could be disputed in multiple ways that could either increase or decrease the reported impact of CKD, and in particular DKD, on the overall health of the population and on the reported costs to the health care system. Physicians routinely use eGFR < 60 mL/min/1.73 m² as a marker of kidney disease, but the formulas are general estimates of GFR (there may 15%-20% variance between GFR estimates and true GFR), and normal aging will result in eGFR < 60 mL/min/1.73 m² in many people. Moreover, it is debatable whether microalbuminuria routinely reflects kidney disease. In addition, the specific impact of DKD on CKD can be questioned because there often is inaccuracy of documentation of medical diagnoses or a patient labeled with DKD may have another diagnosis (eg, hypertension or IgA nephropathy). Any individual patient may have additional processes that can cause kidney disease.

Perhaps a more accurate reflection of the impact of DKD (and CKD) in the United States is seen in end-stage kidney disease data because there is no dispute about the number of people who are receiving dialysis or have a transplant. The number of new end-stage kidney disease cases reported each year has been steady since 2002, but the total number of patients with end-stage kidney disease (prevalence) continues to increase at a rapid rate, with diabetes being the principal cause. Considering that there is greater likelihood of death than progressing to end-stage kidney disease and that mortality rates on dialysis therapy are 15%-20% per year, there must be a very
large CKD population even if the exact number is not well defined.

Race and ethnicity have a major impact on the risk for the development of kidney disease and progression to end-stage kidney disease, also evident in people with end-stage kidney disease caused by diabetes. Rates of end-stage kidney disease due to diabetes in the African American, Native American, and Hispanic populations are increasing, whereas rates have been unchanged for the past 10 years in the white and Asian populations in the United States. The major health disparity needs to be addressed by providers so that screening for signs of DKD is done routinely and aggressive interventions are started as early as possible to slow progression. It is of paramount importance that the nephrology community provides leadership in early diagnosis, best practices, aggressive management, cost-effective interventions, research, and education so that the health care community might slow this epidemic.

Nephrologists do not make the initial diagnosis of DKD; they rely on primary care and endocrinology physicians to make the diagnosis. Thus, a major goal for nephrologists is to provide much wider education to non-nephrology physicians who care for patients with diabetes so that they routinely evaluate for DKD and either institute appropriate treatment or refer to a nephrologist. The diagnosis of DKD usually is based on a clinical history of diabetes, an appropriate sediment (usually bland), and absence of signs and symptoms of another kidney disease. In general, people with type 1 diabetes do not show clinical signs of kidney disease until about 3-5 years after the diagnosis of type 1 diabetes, whereas people with type 2 diabetes may be given a diagnosis of DKD at any time. Using a definition of DKD as microalbuminuria, overt proteinuria, decreased GFR, or end-stage kidney disease in patients with diabetes, the prevalence of DKD in patients with type 1 diabetes may be as high as 50%, but lower in patients with type 2 diabetes.

There essentially are 3 reasons to perform biopsy on a patient with diabetes and kidney disease: diagnosis, prognosis, and research purposes. There is no clinical indication to determine whether a patient with diabetes primarily has DKD or hypertensive kidney disease because the treatment is the same. As for IgA nephropathy, there may be a reason to biopsy if a patient has a urinary protein excretion $> 1 \text{ g}$ and eGFR $> 60 \text{ mL/min} / 1.73 \text{ m}^2$ because recent research has shown that intervening in the appropriate patient may slow progression. There may be indications for biopsy if the patient or physician wants to know the extent of scarring. Routine prognostic biopsy currently is not indicated in DKD. However, with new therapeutic approaches, knowing the degree of damage perhaps will be important for determining the utility, timing, or efficacy of a particular drug therapy. Biopsy for research purposes is an important issue; most biopsy studies have been performed in patients with type 1 diabetes and much less is known about DKD pathology in type 2 diabetic nephropathy. In 2010, the Research Committee of the Renal Pathology Association tackled the issue of pathologic classification of DKD, with the goal of producing a uniform classification system. This and the development of future targeted therapies might be assisted through tissue biobanks. We should consider whether we could enhance our knowledge and improve patient care by performing more biopsies on patients with diabetes.

Regarding treatment, the primary interventions that slow the progression of DKD are control of glycated hemoglobin (HbA1c; goal of $< 7.0\%$), control of blood pressure (BP; goal of $< 130/80 \text{ mm Hg}$), smoking cessation, and lowering of urine albumin levels. Weight loss also may play an important role in the prevention and slowing the progression of DKD. There currently are a number of challenges and shifting ideas about clinically important issues for the treatment of DKD. Data suggest that lower BP (to an extent) better preserves kidney function, but each patient should have individualized BP goals. A general goal of BP $< 130/80 \text{ mm Hg}$ should be targeted in patients with DKD unless there is significant concomitant cardiovascular disease or microalbuminuria alone with normal GFR.

There currently is little or no indication for the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the prevention of DKD in patients with diabetes and normal urine albumin excretion and BP. They offer reasonable first-line treatment for patients with hypertension and normal urine albumin levels; however, selection of antihypertensive agents should be made on an individual basis, taking into account factors such as comorbid conditions, cost, and patient adherence to treatment. It is appropriate to use ACE inhibitors or ARBs in patients with microalbuminuria to help prevent the progression to macroalbuminuria. For overt proteinuria ($> 300 \text{ mg/g}$ of urine albumin), there is a clear indication for treatment with ACE inhibitors or ARBs. Multiple studies using a combination of an ACE inhibitor and ARB therapies suggest little benefit and possibly harm.

Aldosterone inhibition, when added to an ACE inhibitor or ARB, conveys a significant decrease in proteinuria. Although treatment is associated with an increased risk of hyperkalemia, the overall benefit of aldosterone inhibition appears to outweigh the risks. There are no long-term studies that show a definitive
Challenges in Diagnosis and Management of DKD

INTRODUCTION

The number of people with diabetic kidney disease (DKD) continues to increase and is responsible for a large proportion of the practice of all nephrologists. If present trends continue, DKD could soon account for >50% of the patients in dialysis units. Hence, there is an overwhelming need to implement treatments that will either prevent the development of DKD or significantly slow the progression. Research during the past 40 years has led to major advances in early diagnosis and management and has led to treatments to prevent or slow the progression of DKD, yet current approaches clearly are not adequate because the number of patients who develop DKD and the number of patients with progressive DKD continue to increase. Several recent reviews discuss current treatment options in great detail. Many controversies remain regarding standard approaches to patients with both diabetes and renal disease. The intent of this review is to discuss some of the clinically important challenges associated with the diagnosis and management of DKD.

EPIDEMIOLOGY: HOW PREVALENT IS DKD?

Chronic kidney disease (CKD; defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m² or urine albumin-creatinine ratio > 30 mg/g) is estimated to affect 13.1% of the US population, according to the 2012 US Renal Data Survey (USRDS) report. Diabetes is the most prevalent cause of end-stage kidney disease, with hypertension second in the cohort in 2005-2010. Data from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, report that there are approximately 22 million people in the United States with diabetes. Moreover, the CDC estimates that 1 in 3 adults in the United States will have diabetes by 2050 if current trends continue. Based on NHANES III (Third National Health and Nutrition Examination Survey) data, 19.3% of all people with diabetes had GFRs < 60 mL/min/1.73 m², 29.9% had urine albumin-creatinine ratios > 30 mg/g, and 8.6% of all patients with diabetes had both. For those reporting hypertension without diabetes, reported prevalences for the signs of CKD were 12.9% for eGFR < 60 mL/min/1.73 m², 14.8% for urine albumin level > 30 mg/g, and 4.1% for both. However, these estimates may not accurately reflect the prevalence of DKD for several reasons. The data for the CKD population could be disputed in multiple ways that could either increase or decrease the reported impact of CKD, and in particular DKD, on the overall health of the population, as well as on reported costs to the health care system.

First, one could question the accuracy of documentation of medical diagnoses (diagnosis code selection, diagnosis code documentation, time over which diagnostic codes are selected, and others). Current coding allows separate codes for diabetes, CKD stages, and proteinuria, as well as combined codes for diabetes with kidney disease (subcategorized into type 1 and type 2 diabetes). Hence, there may be bias in which code(s) the clinician selects and which codes are selected by the researcher for studies. Research results could be affected by the tools, software, databases, and parameters that researchers select to determine the incidence and prevalence of DKD.

Second, any individual patient may have additional processes that can cause kidney disease. The most common cause of kidney disease in patients with diabetes (other than diabetes) is hypertension, but other entities such as IgA nephropathy also may be present. For example, one study was designed to evaluate the presence of kidney disease in patients who had been given a diagnosis of DKD to determine whether nondiabetic kidney disease was observed. Sixty-six kidney biopsies from patients with diabetes showed that 10 had significant deposits of IgA consistent with IgA nephropathy (6 had type 1

In the past 30 years, there have been significant improvements in slowing the progression of and preventing DKD, yet DKD is a major and increasing worldwide public health concern. The primary goals of the health care system need to be the prevention and slowing of progression of DKD, as well as identification of those at risk for the development and progression of DKD. Further education is required across all health care providers to understand the scope of the problem, implement interventions that prevent the development of DKD, ensure proper screening, understand how to diagnose, and improve knowledge of treatments and when to refer to nephrology.
diabetes and 4 had type 2 diabetes). Any type of kidney disease can occur in patients with diabetes, but depending on the country of origin of the study, other biopsy-proven diseases in addition to IgA nephropathy are focal and segmental glomerulosclerosis, minimal change disease, and interstitial nephritis. Therefore, only routine kidney biopsies can definitively differentiate the cause of kidney disease in diabetes. Clinically, one usually would not perform a kidney biopsy to differentiate DKD from hypertensive kidney disease because it would not affect prognosis or treatment. However, from an epidemiologic and clinical research perspective, the lack of a precise diagnosis is important in that the assumption that the scientist is evaluating DKD may not be fully accurate.

Third, physicians generally use eGFR < 60 mL/min/1.73 m² as a marker of kidney disease. There are 2 matters to consider here. First, the equations used to estimate GFR are not accurate reflections of GFR, but rather general estimates. In one study in which GFR estimates from the Cockcroft-Gault, MDRD (Modification of Diet in Renal Disease) Study, and CKD-EPI (CKD Epidemiology Collaboration) equations were compared with measured GFRs using iothalamate clearances (271 participants), the mean absolute difference from measured GFR ranged from 12-15 mL/min/1.73 m². The authors found that the accuracy (bias was described as the mean difference between estimated and measured kidney function) of all the equations was affected by age (generally more accurate at older age), GFR level affected the MDRD Study and CKD-EPI creatinine estimates (absolute bias was greater in patients with higher GFRs), and weight or body mass index (BMI) affected the accuracy of the Cockroft-Gault formula (absolute bias was greater in patients with higher weight or BMI). These equations serve to inform the clinician of the relative level of kidney function, which enables more accurate estimates of prognosis, risk for complications of kidney disease, need for intervention, drug dosing, risk of dye studies, etc. However, the inherent lack of precision of these equations must be considered in the context of research studies. The second consideration to bear in mind is that normal aging will result in an eGFR < 60 mL/min/1.73 m² in many people. Thus, should everyone with eGFR < 60 mL/min/1.73 m², irrespective of age, be classified as having significant CKD? Perhaps it would be better to select age-appropriate targets for the definition of stage 3 CKD. For example, GFR < 60 mL/min/1.73 m² is an appropriate indicator for those 50 years or younger, whereas the definition of stage 3 CKD should be eGFR < 45 mL/min/1.73 m² in people older than 50 years.

Perhaps a more accurate reflection of the impact of DKD (and CKD) in the United States is seen in end-stage kidney disease data. This is because there is no dispute about the numbers of people who are receiving dialysis or have a transplant. In 1978, there were about 35,000 dialysis patients and about 6,000 transplant recipients. As of 2010, there were approximately 415,000 dialysis patients and 180,000 transplant recipients. The incidence of end-stage kidney disease has increased from 86.8 per million to 347 per million cases per year. Of interest, incidence rates of end-stage kidney disease had been increasing steadily up to 2002, but have remained almost stable since, although the prevalence continues to increase. There has been a slowing of incidence rates of end-stage kidney disease due to diabetes when corrected for the increase in patients with diabetes. Many studies have documented that a person with CKD and declining GFR is much more likely to die of a cardiovascular event rather than surviving to receive dialysis or a transplant for diabetic nephropathy in type 2 diabetes. A recently published study determined that patients with diabetes with CKD compared to nondiabetic kidney disease have much higher death rates for a given level of GFR. Hence, there is a close correlation between GFR and mortality in patients with type 2 diabetes. The authors concluded that all excess mortality in the type 2 diabetes population compared to the population without diabetes is associated with declining GFR. Another recent study from the United States showed that 51% of dialysis patients are alive 3 years after starting dialysis therapy and 82% who received a preemptive transplant are alive at 3 years. Taking this information together, there must be a very large number of patients with CKD (and patients with CKD with diabetes) because the dialysis and transplant patient numbers continue to increase every year.

Since 1990, the rate of end-stage kidney disease cases due to diabetes has increased at a significantly higher rate than any other cause (hypertension cases also have increased, but at a much lower rate; Fig 1). As noted, the number of new end-stage kidney disease cases per year has been steady since 2002, but the total number of patients with end-stage kidney disease (prevalence) continues to increase at a rapid rate, with diabetes being the principal cause (Fig 2). There is some hope that this trend might not continue because there are recent reports suggesting that this rapid increase may be slowing. Whether these reports reflect a true slowing of new cases or just a temporary lull will become evident over the next 5-10 years.

Another important issue to consider in appreciating the impact of DKD is the effect of race and ethnicity. In the United States, this becomes evident by regional differences in the incidence of end-stage kidney disease. The Southern United States, from
Southern California to Southern Texas, has an especially high incidence of end-stage kidney disease, as does the Midwest (rates ranging from 450-950 cases per million in these areas compared with 200-300 cases per million in other regions). This likely reflects the important finding that race and ethnicity have a major impact on risk for the development of kidney disease and the progression to end-stage kidney disease. The racial and ethnic disparities that are seen in the overall end-stage kidney disease data also are evident in the people with end-stage kidney disease caused by diabetes (Fig 3). Although the white population has the highest overall number of patients with end-stage kidney disease in the United States, African Americans have the highest incidence rates per capita (Fig 3). Additionally, Native Americans and people of Hispanic origin have significantly higher incidence and prevalence rates per capita compared with the white population (Figs 3 and 4).

Rates of end-stage kidney disease due to diabetes in the African American, Native American, and Hispanic populations, especially in younger age groups, are increasing, whereas rates have been unchanged for the past 10 years in the white and Asian populations in the United States. This major health disparity needs to be addressed by providers, by recognizing who is at risk so that screening for any signs of DKD is done routinely and aggressive interventions are started as early as possible in order to slow progression. Research to address these issues is ongoing, but more is required to understand the underlying mechanisms responsible for this health disparity.

The financial costs of the end-stage kidney disease population are staggering. The approximately 595,000 patients who are either receiving dialysis or have a transplant constitute ~0.2% of the US population. This patient population cost Medicare $30 billion in 2010, which is almost 6% of the annual Medicare budget. In this era of rapidly increasing health care costs, lawmakers certainly will be paying significant attention to very expensive services. The personal burden of the combination of diabetes and kidney disease includes decreased quality of life and increased financial costs. It is of paramount importance that the nephrology community provide leadership in early diagnosis, best practices, aggressive management, cost-effective interventions, research, and education so that the health care community as a whole might work together to slow this epidemic.

A sobering statistic in the USRDS data is that nephrologists do not make the initial diagnosis of DKD; they rely on primary care and endocrinology physicians to make the diagnosis. In 2010, a total of 43% of patients started dialysis therapy without ever seeing a nephrologist. Even when patients were known to have diabetes, 38.9% started dialysis therapy without ever seeing a nephrologist. This means it is likely that providers were not adequately screening patients and did not recognize declining kidney function. It does not mean that nephrologists need to...
see every patient with a GFR < 60 mL/min/1.73 m² and urine albumin level > 30 mg/g, but that non-nephrologists need to routinely screen by calculating eGFR and measuring urine albumin-creatinine ratios in patients with diabetes. Referral should occur if eGFR is declining (<45 mL/min/1.73 m² should at least prompt a screening visit to a nephrologist) and urine albumin levels are increasing, certainly if urine albumin-creatinine ratio is >300 mg/g (or urine protein-creatinine ratio is >0.5 g/g). Thus, another major goal for nephrologists to achieve is to provide much wider education in many different forms to non-nephrology health care practitioners who care for patients with diabetes so that they routinely evaluate for DKD and either institute appropriate treatment or refer to a nephrologist for diagnosis and concomitant care.

**DIAGNOSIS: IS A KIDNEY BIOPSY INDICATED?**

The diagnosis of DKD usually is based on a clinical history of diabetes and an appropriate sediment (generally bland, but a small number of red blood cells may be present) and absence of signs and symptoms of another kidney disease. In general, people with type 1 diabetes do not show clinical signs of kidney disease (decreased GFR and/or increased urine albumin-creatinine ratio) until about 3-5 years after the diagnosis of type 1 diabetes, whereas in people with type 2 diabetes, DKD may be diagnosed at any time. Estimates of the prevalence of DKD vary widely and range from 10%-40% for both type 1 and type 2 diabetes patient groups, depending in part on the definition of the disease. In general, using a definition of DKD as microalbuminuria, overt proteinuria, decreased GFR, or end-stage kidney disease in patients with diabetes, the prevalence of DKD in patients with type 1 diabetes may be as high as 50%, but lower in patients with type 2 diabetes. A recent study from Spain determined a DKD prevalence of 27.2% in patients with type 2 diabetes. So when is a biopsy indicated in a patient with diabetes and kidney disease?

There are essentially 3 reasons to biopsy: diagnosis, prognosis, and for research purposes. First, from a diagnostic perspective, it always is important to consider diseases other than diabetes as the cause of kidney disease in patients with diabetes and kidney disease. In the United States, the most common diseases that cause non-diabetic kidney disease in people with diabetes (and reasonably bland sediment) are hypertension and, less commonly, IgA nephropathy. There is no clinical indication to determine whether a patient with diabetes primarily has DKD or hypertensive kidney disease because the treatment is the same. As for IgA nephropathy, there may be a reason to biopsy if a patient has a urinary protein excretion > 1 g and eGFR > 60 mL/min/1.73 m² because recent research has shown that intervening with steroids in the appropriate patient may slow progression. The decision to biopsy also is affected significantly by other factors, such as the likelihood of...
discovering another kidney disease in a specific population. For example, in China, where the estimated prevalence of CKD is about 10%-11%, primary glomerulonephritis (mostly IgA nephropathy) is the major cause of CKD (~40% of all cases of CKD), with DKD being a smaller percentage (~10%). However, new research suggests that the ongoing epidemic of diabetes in China will lead to a very substantial increase in DKD.

Other diagnostic reasons to perform biopsy on patients with diabetes are rapidly declining eGFR, rapidly increasing urine protein or very high protein level, active urinary sediment, signs or symptoms suggestive of a nondiabetic cause for kidney disease, concerns that a medication might be causing reduced kidney function (eg, interstitial nephritis), or a sudden change in eGFR, urine albumin excretion, or urine sediment in a patient with known DKD. Of note, the absence of diabetic retinopathy in the absence of other indications is not a reason to biopsy. Although it used to be stressed that the lack of diabetic retinopathy indicates a high likelihood for a nondiabetic cause of kidney disease, it now is clear that this is not the case, especially in patients with type 2 diabetes and kidney disease. For example, a study of 323 patients with type 1 diabetes and 906 patients with type 2 diabetes determined that a majority of patients with type 1 diabetes and macroalbuminuria had some retinopathy, whereas 47.5% of patients with hypertension and type 2 diabetes with overt proteinuria did not have retinopathy. Therefore, the absence of diabetic retinopathy in a patient with DKD should raise the question of whether the kidney disease process is due to a disease other than diabetes, especially in people with type 1 diabetes. However, if there are no other supporting signs or symptoms from the patient’s history, physical, or laboratory results, there usually is little indication for biopsy.

Also relevant to the use of biopsy for diagnosis, the absence of an increase in urine albumin level despite decreasing GFR is not necessarily an indication for biopsy. Although it is common for urine albumin level to increase prior to any decrease in GFR, it now is well established, especially in patients with type 1 diabetes, that GFR can decrease independently of urine albumin level. In a study of 103 patients with normoalbuminuric type 1 DKD, patients underwent biopsy for research purposes and were stratified into normal (mean, 121 mL/min/1.73 m²) or low (mean, 75 mL/min/1.73 m²) eGFR categories. Evaluation of the biopsy specimens revealed multiple signs of diabetic nephropathy (ie, thickened glomerular basement membrane and mesangial expansion). Another study designed to assess the predictive value of microalbuminuria as a predictor for pathologic changes consistent with DKD in patients with type 1 diabetes revealed that there was a significant increase in pathologic indicators of DKD in the group with persistent microalbuminuria (ie, increased glomerular basement membrane thickness) compared with other groups (eg, intermittent microalbuminuria) over a 5-year period. However, 64% of research participants had reversion of microalbuminuria to normoalbuminuria. This may reflect improvement in pathology or possibly a disconnect between albuminuria and pathology. Other researchers have reported similar findings in patients with type 1 diabetes, including reversion of microalbuminuria to normoalbuminuria and disconnect between level of albuminuria and rate of GFR decline; that is, GFR may decline in the absence of albuminuria. Similar findings have been reported in patients with type 2 diabetes. The DEMAND (Developing Education on Microalbuminuria for Awareness of Renal and Cardiovascular Risk in Diabetes) Study evaluated a large cohort of patients with type 2 diabetes (32,208 patients aged 18-80 years). The authors reported that CKD was noted in 17% of those with normoalbuminuria (CKD stages 3-5), and significantly reduced kidney function was found in 27% of those with microalbuminuria and 31% of those with overt proteinuria. Creatinine clearance was <60 mL/min/1.73 m² in 20.5% of those with normoalbuminuria, 30.7% of those with microalbuminuria, and 35.0% of those with macroalbuminuria. Hence, in patients with either type 1 or type 2 diabetic nephropathy, increasing urine albumin levels are associated with declining GFR, but it also is clear that people with diabetic nephropathy may have reduced GFR and normal urine albumin levels. Therefore, a patient with diabetes, declining GFR, and normal urine albumin level does not necessarily have a clinical indication for biopsy unless there are other signs or symptoms that suggest a disease other than diabetes.

As for prognosis, there may be indications for biopsy if the patient or physician wants to know the percent of scarring. The level of albuminuria may not correlate with severity of disease and the inherent variability of eGFR may not accurately reflect the degree of damage to the kidneys. There are not many studies that relate test values to kidney damage; however, a study from 2005 reported on biopsies from 105 patients with diabetic glomerulosclerosis and followed up for 56 months. The prognostic values (how many progressed to dialysis therapy) of duration of diabetes, creatinine level, proteinuria, and histologic score were evaluated. Serum creatinine level and histologic score were statistically significant predictors, whereas duration of diabetes and proteinuria were not. A routine prognostic clinical biopsy currently is not indicated in patients with DKD. However, with new therapeutic approaches, knowing
the degree of damage perhaps will be important for determining the utility, timing, or potential efficacy of administering a particular drug.

Biopsy for research purposes is an important issue. There has been much discussion about the pathologic natural history of DKD. Glomerular basement membrane thickening is considered to be the earliest measurable sign of DKD, followed by expansion of the mesangial matrix and hyalinosis of the afferent and efferent arterioles.40 Most longitudinal biopsy studies have been performed in patients with type 1 diabetes,40 and much less is known about DKD pathology in type 2 diabetic nephropathy. Furthermore, there is significant interest and growing data on potential roles for tubulointerstitial disease as an initiating factor of DKD.41-43 Biopsy material potentially could help determine how important tubulointerstitial disease is in the pathogenesis and progression of diabetic nephropathy. It also is not clear what cells in the glomerulus are primarily at risk for the damage caused by hyperglycemia: the glomerular endothelial cell, mesangial cell, podocyte, or a combination. As such, there has been growing interest in establishing tissue biobanks in order to examine diabetic kidneys at all stages of the disease to answer these important pathophysiologic questions. Clearly determining the cell type or types at risk (along with determining underlying mechanisms) will provide necessary information that can be used for the development of future targeted therapies.

In 2010, the Research Committee of the Renal Pathology Association tackled the issue of pathologic classification of DKD, with the goal of producing a uniform classification system that would assist in ascribing uniform chronicity and staging criteria for clinicians and researchers.44 The committee proposed 4 stages (Table 1), with glomerular basement membrane thickening as class I and advanced glomerulosclerosis as class IV. Of note, degree of interstitial fibrosis (scored 0-2), interstitial inflammation, and vascular lesions (Table 2) also were included. The researchers reported very good interobserver variability when using these criteria. To test their system, 5 pathologists classified 25 biopsy specimens and found an intraclass correlation coefficient of 0.84. This classification is important for all nephrologists to know because it provides a potential framework for clinical prognosis and research. Only with sufficient material will further insights into the pathogenesis, prognosis, and interventions of DKD be achieved. To date, there have been no truly successful animal models of DKD, although many have been working on this.45 Thus, we should consider whether we could enhance our knowledge and improve patient care by performing more biopsies on patients with diabetes.

**TREATMENT CONTROVERSIES**

**Overview**

The primary interventions that slow the progression of DKD are control of glycated hemoglobin (HbA1c) levels,46-51 control of blood pressure (BP),52-55 smoking cessation,56,57 and lowering of urine albumin levels.58-63 Furthermore, weight loss60,61 also may play an important role in prevention and slowing the progression of DKD. Blood glucose management issues are discussed in detail elsewhere in this supplement.62 Two excellent reviews of overall BP management in patients with diabetes or diabetic nephropathy, as well as thoughtful discussions about albuminuria management, recently have been published.63,64 The first focuses on “optimal” antihypertensive therapy in patients with type 2 diabetes and hypertension and discusses areas of uncertainty.65 The second discusses the mechanisms involved in
There are considerable data supporting an essential role of achieving BP goals in patients with DKD for both primary prevention and slowing of disease progression. The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)-recommended goal for BP in patients with diabetic nephropathy is <130/80 mm Hg. However, recent studies have prompted some major organizations, such as the American Diabetes Association, to alter their guidelines for BP goals from 130/80 to 140/80 mm Hg, which may have an impact on the primary prevention of DKD. The impetus for these changes came primarily from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study. ACCORD was a prospective, randomized, multicenter clinical trial of 4,733 patients with type 2 diabetes who were followed up for an average of 4.7 years. The study was designed to assess the multiple interventions on cardiovascular outcomes in high-risk patients with diabetes, including the benefits of intensively treating BP (<120 mm Hg) versus conventional treatment (140 mm Hg). The primary outcome was first occurrence of a major cardiovascular event, defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The study found no beneficial effect of intensive BP control (systolic BP [SBP] < 120 mm Hg) on risk of myocardial infarction or cardiovascular death, although it found significant lowering of stroke risk. From a diabetic nephropathy perspective, it is important to note that the vast majority of patients in this study did not have DKD (mean GFR, 91.6 mL/min/1.73 m², and mean urine albumin-creatinine ratio, 14.5 mg/g). The INVEST (International Verapamil-Trandolapril Study), in which patients were 50 years or older and had diabetes, also showed no benefit of lowering SBP beyond the goal of <140 mm Hg (significantly decreased kidney function was present in ≤5% in the INVEST group).

Conversely, a number of studies have found that for patients with DKD, BP < 130/80 mm Hg delayed the progression of kidney disease. For example, a BP analysis of the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) Study in patients with type 2 diabetes determined that those with SBP < 140 mm Hg had significantly improved outcomes. Likewise, an analysis of multiple studies correlated significant slowing of loss of GFR as BP decreased (Fig 5). Although these data suggest that the lower the BP, the better preserved the kidney function, there is reason not to lower it too much. In the IDNT (Irbesartan Diabetic Nephropathy Trial), SBP ≤ 120 mm Hg was associated with an increase in all-cause mortality and cardiovascular mortality compared with those with higher BP. Of note, ~60% of participants had cardiovascular disease. In a subgroup analysis of 6,400 patients in INVEST, increased cardiovascular mortality was observed in participants with SBP < 115 mm Hg (Fig 6).

**Hypertension Management: What Is the BP Target?**

Hypertension in patients with diabetic nephropathy and reviews clinical trials using single agents as therapeutics and trials involving novel drugs or drug combinations used to treat these patients. However, there currently are a number of challenges and shifting ideas on clinically important issues for the treatment of DKD, and they are addressed next.

### Table 2. Recently Revised Pathologic Classification of Interstitial and Vascular Lesions in Diabetic Kidney Disease

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Criteria</th>
<th>Score</th>
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<tr>
<td>Interstitial lesions</td>
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<tr>
<td>IFTA</td>
<td>No IFTA</td>
<td>0</td>
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<tr>
<td>&lt;25%</td>
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<td>1</td>
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<td>25%-50%</td>
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<td>&gt;50%</td>
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<td>Interstitial inflammation</td>
<td>Absent</td>
<td>0</td>
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<td>Infiltration only in relation to IFTA</td>
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<td>1</td>
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<tr>
<td>Infiltration in areas without IFTA</td>
<td></td>
<td>2</td>
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<tr>
<td>Vascular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriolar hyalinosis</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>At least 1 area of arteriolar hyalinosis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>More than 1 area of arteriolar hyalinosis</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Presence of large vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteriosclerosis (score worst artery)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No intimal thickening</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Intimal thickening less than thickness of media</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Intimal thickening greater than thickness of media</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: IFTA, interstitial fibrosis and tubular atrophy. Reproduced with permission of American Society of Nephrology from Tervaert et al.
There is a growing recognition that BP goals need to be targeted to the individual patient. In patients with coronary artery disease, lowering SBP to <140 mm Hg likely is sufficient and lowering to <120 mm Hg appears to lead to worse outcomes. However, although lower BP reduced the risk of stroke in the ACCORD Study, this effect was not observed in INVEST. Furthermore, SBP < 130 mm Hg leads to improved kidney-related outcomes in patients with DKD. Thus, the ideal BP for a patient with diabetes needs to be tailored to the patient. A general goal of <140/80 mm Hg should suffice provided the patient has no evidence of DKD. However, a goal of <130/80 mm Hg should be targeted in patients with DKD unless there is significant concomitant cardiovascular disease or microalbuminuria alone with normal GFR.

**Renin-Angiotensin-Aldosterone Axis: Focus on Angiotensin II Inhibition**

Many studies have demonstrated increased activity in the renin-angiotensin-aldosterone system (RAAS) in patients with diabetes and patients with DKD. Blockade of this system (especially of angiotensin II) has been the mainstay of DKD treatment for 30 years. A number of recent studies have provided further insights into the best use of these medications.

**What Is the Mechanism of Action for ACE-Inhibitor and ARB Medications?**

The effects of blockade of the RAAS on angiotensin II and glomerular pressures has generated much attention because decreased angiotensin II leads to vasoconstriction of the efferent arteriole with a resultant decrease in glomerular pressure gradient across the basement membrane and a subsequent decline in GFR. This decrease in intraglomerular pressures has been presumed to be the primary mechanism by which these medications work; there certainly is evidence for this from animal studies. However, animal studies are problematic because all animal models of DKD to date are thought to not accurately reflect human DKD. In addition, the measurements (whether single-nephron GFR using micropuncture techniques or by whole-animal clearance studies) are snapshots and may be misleading. Angiotensin II has multiple other actions, including stimulation of inflammation by stimulation of factors such as transforming growth factor β, activation of NADPH (reduced nicotinamide adenine dinucleotide phosphate) oxidase, and other effects, all of which may be mechanistically important to angiotensin II-mediated damage to the kidney. Moreover, these medications may have actions independent of angiotensin II that are beneficial. For example, the enzyme kininase II is the same enzyme as angiotensin-converting enzyme (ACE); hence, ACE inhibitors may alter 2 pathways: the RAAS and the bradykinin pathway. Kininase II blockade leads to the increase in bradykinin levels that is thought to be responsible for the cough seen in some patients receiving an ACE inhibitor. Additionally, increasing bradykinin levels may play a beneficial role in kidney disease progression. These medications have been of significant benefit in the treatment of patients with proteinuria and DKD. Determining the exact mechanism by which they work may lead to an even more effective treatment.

Regardless of the exact mechanism, it has been determined that the decrease in GFR seen with ACE-inhibitor/angiotensin receptor blocker (ARB) treatments is at least an important indicator of their effectiveness in slowing the progression of DKD. Bakris et al reviewed this issue and reported that an increase in serum creatinine level of up to 30% within the first 4 months of starting ACE-inhibitor treatment (baseline up to 3 mg/dL) correlated with slower rates of decline in kidney function after 3 or more years of follow-up (Fig 7). In a recent subanalysis of the RENAAL Study, in which losartan was given to patients with type 2 diabetes to determine whether it slowed disease progression, the authors found that the greater the initial decline in GFR, the slower the rate of progression of DKD (Fig 8). This important finding emphasizes the need to monitor GFR after prescribing these medicines. Measuring GFR (and potassium) after starting treatment with an ACE inhibitor or ARB anew or after increasing the dose may be needed not only to determine whether GFR has declined too much (or potassium increased too much), but also to determine whether GFR has declined at all. Hence, irrespective of whether the protective effects of angiotensin II inhibition are due to lowering of glomerular pressures, the decrease in...
GFR directly reflects the efficacy of the medications. It is important to educate non-nephrology physicians and counsel patients in the proper use of these medications because too often these medication treatments are stopped when GFR decreases.

Are ACE Inhibitors and ARBs Effective for Primary Prevention of DKD?

This question has received considerable attention during the past 10 years due to the public health implications of suggesting that all patients with diabetes be placed on ACE-inhibitor or ARB therapy for the primary prevention of DKD. Two recent detailed analyses have come to different conclusions. The Cochrane review recommends the use of ACE inhibitors (though not ARBs; the authors state that to date, studies do not support use of ARBs for primary prevention) for primary prevention in normotensive normoalbuminuric patients, whereas the NKF-KDOQI guidelines recommend against using these medications in this clinical scenario. The Cochrane review stated the following: “We identified 26 studies enrolling 61,264 participants. ACE-Is reduced the risk of new onset of microalbuminuria, macroalbuminuria or both when compared to placebo (eight studies, 11,906 patients: RR 0.71, 95% CI 0.56 to 0.89), with similar benefits in people with and without hypertension (P = 0.74). The weight of this recommendation is based primarily on albuminuria. NKF-KDOQI reviewed many of the same studies, but was swayed more by the lack of definitive evidence for such outcomes as differences in pathologic signs of DKD. For example, with respect to ACE inhibitors and ARBs for primary prevention in type 1 diabetes, researchers studied 285 patients with type 1 diabetes and no evidence of DKD who were treated with enalapril, losartan, or placebo for 5 years. At the beginning of the study, 90% of patients had a kidney biopsy that was repeated 5 years later. The study showed that neither losartan nor enalapril prevented the development of microalbuminuria. Likewise, the biopsy data showed that there was no prevention of early signs of DKD (Table 3). The strength of the conclusions was greatly enhanced because the study involved biopsy material.

There are conflicting study results regarding the use of ARBs for primary prevention. One large study in which candesartan was prescribed to prevent the development of microalbuminuria in patients with diabetes showed no benefit. Study participants were normoalbuminuric and mostly normotensive in 3 separate clinical trials that included a total of about 3,300 people with type 1 diabetes and 1,900 with type 2 diabetes. The study showed no benefit for prevention of the development of microalbuminuria during a 4.7-year period.

Although the Cochrane review and NKF-KDOQI guidelines differ in the utility of ACE inhibitors for primary prevention, they agree on the lack of utility of ARBs in primary prevention. Some large studies of patients with type 2 diabetes have shown a benefit in slowing the development of albuminuria. However, the estimated development of microalbuminuria ranges from 10%-40% in patients with type 2 diabetes, which means that 60%-90% will not develop...
microalbuminuria.2,24-26 This would mean there would be a significant number of individuals taking a medication they do not need. It is not clear at this time whether prescribing an ACE inhibitor or ARB to all patients with type 2 diabetes without kidney disease and hypertension would cause more harm or good. If the patient is hypertensive, an ACE inhibitor or ARB may be the best initial medication.

**Should ACE Inhibitors and ARBs Be Used in Combination?**

There were a number of studies showing the benefits of ACE inhibitors used in combination with ARBs for the treatment of DKD.80-85 A meta-analysis published in 2007 reviewed these studies and concluded that there was therapeutic benefit to using the combination, but cautioned that their findings may be misleading by noting that many of the studies were of short duration.84 In 2008, ONTARGET (Ongoing Telmisartan Alone and in Combination With Ramipril Global End-point Trial) changed attitudes about using the combination of ACE inhibitors and ARBs.86 ONTARGET compared the efficacy of telmisartan and ramipril in combination with that of telmisartan or ramipril monotherapy with the intent of showing noninferiority of telmisartan compared to ramipril. This large study, about 25,500 participants, showed that the combination was not superior to using these medications alone. There appeared to be more adverse events (decreased GFR and hyperkalemia) in patients using the combination compared with those on monotherapy. This large well-done study led many to conclude that physicians should not use these medications in combination. The ONTARGET population consisted of 38% with diabetes and 13% with microalbuminuria, and the average GFR decreased to within the normal range. Thus, the relevance of ONTARGET to the population of patients with stage 3 (GFR < 60 mL/min/1.73 m²) or worse CKD and macroalbuminuria (the patient cohort with the highest risk for progression to end-stage kidney disease) was unclear. To answer this issue, a subgroup analysis of ONTARGET was performed to determine whether combination therapy improved outcomes in participants with decreased GFR and/or increased urine albumin level. Overall, the study did not show a benefit for combination therapy and may even have led to worse outcomes. This analysis concluded that dual blockade likely is not better than monotherapy and the combination may well have been detrimental. However, the cause of the kidney disease in this population was not clear (it was not specifically evaluated).87

A recent study was published that evaluated the effect of the combination of lisinopril and irbesartan versus lisinopril or irbesartan monotherapy in patients with type 2 diabetes and average GFR of ~48 mL/min/1.73 m² at maximal dose with the study end points of >50% increase in serum creatinine level, end-stage kidney disease, and death over a 4-year period.88 Results showed no benefit of the combination therapy compared to monotherapy, and there were no differences in adverse events. Although this is one of the first studies to address this issue in type 2 diabetes, it has limitations, as the authors noted (the study included only 133 patients, mostly men, with a mean age of 67 years). The study was not double blind and the outcome event rate was lower than expected in all groups. Because a number of studies have demonstrated the benefit of lowering albumin excretion in patients with microalbuminuria for slowing the progression of DKD,15,58,89 it is justifiable to use a variety of methods to lower urine albumin levels. Two debates published in 2010 provide excellent discussions of the pros and cons of using an ACE inhibitor and an ARB in combination for the treatment of CKD.90,91 A meta-analysis recently was published that addressed the specific question of whether there is support for using dual RAAS blockade for treating patients with DKD.85 The detailed analysis concluded that dual blockade should be used in patients with diabetes, macroalbuminuria, and normal potassium levels. Recently, 2 long-term studies were designed to develop better understanding of the role of combination therapy in

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**Table 3. Effects of Enalapril or Losartan Treatment on Primary Prevention of Development of an Early Pathologic Lesion of Diabetic Kidney Disease**

<table>
<thead>
<tr>
<th>End Point (mesangial fractional volume)</th>
<th>Enalapril</th>
<th>Losartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean at baseline</td>
<td>0.201 ± 0.044</td>
<td>0.189 ± 0.041</td>
<td>0.187 ± 0.045</td>
</tr>
<tr>
<td>Mean change at 5 y</td>
<td>0.005 ± 0.050</td>
<td>0.026 ± 0.054</td>
<td>0.016 ± 0.048</td>
</tr>
<tr>
<td>Change vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean difference</td>
<td>-0.011</td>
<td>0.010</td>
<td>0 (reference)</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.16</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Adjusted change vs placebo</td>
<td>-0.006</td>
<td>0.008</td>
<td>0 (reference)</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>0.38</td>
<td>0.26</td>
<td></td>
</tr>
</tbody>
</table>

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patients with DKD: the VA NEPHRON-D Study, which consists of 1,448 patients with type 2 diabetes and a wide range of GFRs and was scheduled to be completed by October 2014;92 and the VALID (Preventing ESRD in Overt Nephropathy in Type 2 Diabetes) Study, which consists of approximately 100 patients with type 2 diabetes and significant kidney disease, as defined by serum creatinine level of 1.8-3.5 g/dL and urine albumin-creatinine ratio > 1,000 mg/g, and is due to be completed December 2015.93 The VA NEPHRON-D Study was stopped earlier this year by the Data and Safety Monitoring Board due to what was reported as increased acute kidney injury and hyperkalemia events in the dual-blockade cohort, and due to lack of efficacy. This result certainly brings into question the safety and efficacy of dual blockade.

**Should ACE Inhibitors and ARBs Be Discontinued at a Particular eGFR Level?**

There are several acute situations that require at least temporary discontinuation of these medications. Significant side effects should prompt a clinician to stop the medication. However, in the absence of complications and acute events, should these medications be continued until dialysis or transplantation? In 2001, a secondary post hoc analysis of the REIN (Ramipril Efficacy in Nephropathy) trial, consisting of 322 patients with nondiabetic proteinuric CKD and different levels of kidney function, was done to evaluate this question.94 It was found that the best effect for slowing the progression to end-stage kidney disease was achieved in the group with the lowest GFR. Moreover, the earlier ramipril treatment was started and maintained, the better the protection. Furthermore, data from the RENAAL Study with losartan also suggested that prolonged use slows the progression to end-stage kidney disease.95 There have not been many detailed studies about this issue, but in the absence of a reason to stop ACE-inhibitor or ARB treatment in a patient nearing dialysis, it may make sense to maintain the patients on these medications.

**Recommendations for Use of ACE Inhibitors and ARBs in DKD**

1. There currently is little or no indication for the use of ACE inhibitors or ARBs in the prevention of DKD in patients with diabetes and normal urine albumin excretion and BP.
2. They are a reasonable first-line treatment for patients with hypertension and normal urine albumin levels; however, selection of antihypertensive agents should be made on an individual basis, taking into account factors such as comorbid conditions, cost, and treatment adherence.
3. Consider using ACE inhibitors or ARBs in patients with microalbuminuria to help prevent progression to macroalbuminuria.
4. For overt proteinuria (>300 mg/g of urine albumin), there is a clear indication for ACE-inhibitor or ARB treatment. The stopping of VA NEPHRON-D brings into question whether there is any role for combination ACE-inhibitor/ARB treatment for patients with DKD. The VALID Study may be the final arbiter as to whether there is a role for dual blockade in patients with DKD.

An interesting question is whether these medications are of benefit in patients with DKD who have normal albumin levels but decreased GFR. There are few data for this particular scenario. It may be recommended to use these medications if the patient also is hypertensive. However, if complications arise as a result of using these medications (such as hyperkalemia or cough), switching to another antihypertensive agent would be indicated.

**Renin-Angiotensin-Aldosterone Axis: Is There a Role for Renin Inhibition?**

There was much interest when the renin inhibitor aliskiren was launched as an inhibitor of the RAAS.96 One short-term study showed a promising reduction in urine albumin excretion using aliskiren and losartan combination therapy in patients with diabetes.97 As such, aliskiren could be used in combination with either an ACE inhibitor or ARB to lower urine albumin levels and slow progression. ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) was designed to evaluate whether the addition of aliskiren to ACE inhibitor or ARB treatment provided further renoprotective benefits.98 In late 2011, the study was stopped prematurely by the data safety and monitoring board for the study due to the occurrence of excess adverse events (nonfatal stroke, hyperkalemia, hypotension, and decreased kidney function). Considering that generic forms of ACE inhibitors provide a much more cost-effective solution to managing urine albumin levels than aliskiren, the precise role for aliskiren in the treatment of DKD is not clear at this time.

**Renin-Angiotensin-Aldosterone Axis: Focus on Aldosterone Inhibition**

Aldosterone inhibition has been widely underused for DKD treatment. In addition to aldosterone effects on sodium, potassium, and pH regulation, aldosterone leads to increased levels of reactive oxygen species, transforming growth factor β, and plasminogen activator inhibitor and other effects that can lead to glomerular podocyte loss, as well as tubulointerstitial fibrosis.99 Numerous articles have been
published in the cardiovascular literature that discuss the beneficial effects of spironolactone, especially in patients with congestive heart failure and/or cardiovascular disease.101-103 The benefits of spironolactone for CKD, and in particular DKD, have become apparent over the past 10 years.104 There are multiple studies showing a significant decrease in proteinuria when aldosterone inhibition is added to ACE-inhibitor or ARB therapy. Treatment is associated with an increased risk of hyperkalemia, but the overall benefit of aldosterone inhibition may outweigh the risks.104,105 At this time, spironolactone may be considered to possibly be of benefit for patients with DKD. However, there are no long-term studies with spironolactone alone or in combination with other RAAS inhibitors showing improved kidney outcomes. Larger and long-term studies are needed to better understand the relationship between aldosterone inhibition and DKD outcomes.

Do Nondihydropyridine Calcium Channel Blockers Lower Proteinuria and Help Slow the Progression of DKD?

Studies during the past 15 years appeared to show that nondihydropyridine medications (eg, diltiazem and verapamil) slightly decreased proteinuria independently of any BP-lowering effects.106-108 A recent study evaluated the effects of diltiazem on the development of urinary albumin excretion in patients with hypertension and type 2 diabetes, with persistent microalbuminuria despite ACE-inhibitor treatment.109 Thirty-six patients with type 2 diabetes, hypertension, and microalbuminuria persisting after more than 1 year of treatment with ACE inhibitors were randomly assigned to receive captopril (n = 22) or captopril and 120 mg of diltiazem combined therapy (n = 14) for 2 years. There was no increase in albumin excretion in the combined-therapy group, whereas absolute albumin excretion increased in the captopril monotherapy group. The beneficial effects of the addition of diltiazem were independent of BP and metabolic control. More recently, a head-to-head study of patients with type 2 diabetes compared trandolapril/verapamil combination therapy with benazepril/amldipine combination therapy, and both combinations were seen to reduce proteinuria.110 Recommendations at this time are to use either type of calcium channel blocker as an addition to RAAS inhibitors, mostly for BP management. For patients unable to tolerate RAAS inhibitors (usually due to hyperkalemia) for the reduction of proteinuria (not considering antihypertensive actions), there are data supporting the use of nondihydropyridine monotherapy when compared with dihydropyridine monotherapy.

Is There a Role for Pentoxifylline in Treating DKD?

Pentoxifylline is a methylxanthine phosphodiesterase inhibitor that has been used for many years to improve vascular blood flow, but also has been shown to have anti-inflammatory and immunoregulatory effects.111-113 During the past 10 years, pentoxifylline has shown antiproteinuria effects.111-113 All studies to date generally have been small and short in duration and have focused entirely on reduction of proteinuria.111-113 Thus, it is difficult to know the utility of this different class of medication, but it still may find a role in the treatment of DKD.

Protein Intake and DKD: Should Low-Protein Diets Routinely Be Prescribed?

A role for protein in the progression of DKD has been discussed for many years.114 Initial observations illustrated that GFR increases significantly after a high-protein meal.115 Many subsequent studies using animal models of DKD illustrated that a high-protein diet accelerated the rate of increase in urine protein levels and rate of decline in GFR in animal models of DKD.114,115 The primary mechanism (determined by single-nephron GFR micropuncture studies) illustrated that a high-protein diet (50% of the diet was protein compared to a usual rat diet of 12% protein) caused an increase in intracapillary glomerular pressure with a resultant increase in GFR.114,115 A low-protein diet (6% protein in the diet) slowed the decline in GFR and development of proteinuria. These findings led to the MDRD Study,116,117 which was designed to show the benefit of a low-protein diet (<0.8 g/kg/d) in slowing the progression of CKD. Unfortunately, there was no benefit seen in this study. There may be a number of reasons for this, including the length of the study, that there are beneficial effects for certain subgroups that were not seen when examining the entire cohort, and difficulty maintaining a low-protein diet. The MDRD Study had a relatively small subgroup with DKD. Subsequent studies of patients with diabetes have used diets with protein as low as <0.4 g/kg/d (with supplementation of essential amino acids), with most studies using protein lower than 0.6-0.8 g/kg/d.118,119 Almost all these studies have focused on patients with type 1 diabetes, are of short duration, and are small. Although some studies have reported reduced albuminuria, there are no long-term studies that clearly show a definitive benefit for a low-protein diet. An extensive review of protein intake and DKD is beyond the scope of this review, but the published data lead to the following recommendations:

1. There are no long-term data supporting the prescription of a low-protein diet (<0.6-8 g/kg/d) in

Robert C. Stanton

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patients with DKD. The prescribed diet should balance all the patient’s nutritional needs and protein level should be prescribed in this context primarily.

2. A low-protein diet may offer additional benefits, especially in patients who have maximized other therapeutic approaches.

3. There are additional benefits to low-protein diets independent of protein level in that reduced protein intake also is associated with reduced phosphate, sodium, and fat intake and other potentially beneficial effects. One study suggests that the beneficial effect of a low-protein diet might be due primarily to the reduction in sodium intake and subsequent improvement in BP.

4. It is likely that high-protein diets are deleterious. There are no studies of humans definitively showing this, but the work in animal is very compelling. Also, the exact definition of a “high-protein diet” is not clear. Nevertheless, avoiding protein supplements and weight-loss diets that consist of a high-protein component seems prudent for patients with DKD.

Smoking Cessation and DKD

Studies dating back 30 years showed that smoking is a risk factor for both the development and progression of DKD. The data seem to be as relevant for patients with type 1 DKD as for those with type 2 DKD. There also are data suggesting slowing of DKD progression in smokers who quit smoking. Hence, although the data are not extensive or based on large studies, considering the effects of smoking on general health and diabetes specifically, it is strongly recommended that all patients with DKD cease smoking.

Is There a Specific Unique Role for Lipid Management in DKD?

There have been a number of studies revealing an association between hypercholesterolemia and rate of progression of DKD. Elevated serum cholesterol levels are correlated with decreased GFRs in patients with either type 1 or type 2 DKD. Thus, it has been suggested that elevated serum cholesterol level is a risk factor for the progression of kidney disease. Interestingly, in a study that showed regression of microalbuminuria in patients with type 1 diabetes, low cholesterol and triglyceride levels correlated with regression. The FIELD Study evaluated fenofibrate treatment on albuminuria and eGFR and found that during a 5-year period, fenofibrate treatment modestly lowered albuminuria and slowed eGFR decline compared with groups not treated with fenofibrate, especially in patients with hypertriglyceridemia (but no difference in end-stage kidney disease was seen). Fenofibrate increased creatinine levels initially, but this was not maintained, and 2 more recent studies suggest that fenofibrate likely is safe to use in patients with moderate kidney disease. However, more studies clearly are needed to determine whether treatment of cholesterol and/or triglyceride levels will prevent the development or slow the progression of DKD. Thus, no specific recommendation on the benefits of lowering cholesterol and/or triglyceride levels can be made at this time. Perhaps a multifactorial approach to management (that includes lipid management, BP control, blood glucose control, etc) as was done in the STENO-2 Study will provide the best outcomes.

Is There a Role for Weight Loss in DKD?

Obesity has been observed to be a clear risk factor for kidney disease in general and for DKD. Obesity is associated with increased lipid levels, hypertension, endothelial cell dysfunction, and other metabolic abnormalities. Thus, it is not clear whether the main reason obesity is associated with kidney disease are the factors associated with obesity or other factors unique to the obese person, such as release of inflammatory mediators from visceral fat cells. Interestingly, one case report describes resolution of albuminuria following bariatric surgery. It is not clear whether this improvement is due to an intrinsic change in cellular physiology associated with the alteration in body habitus from obese to nonobese or to improved blood glucose and BP control. A recent review discusses the evidence linking obesity to CKD.

CONCLUSION

Much has been learned in the past 30 years that has led to significant improvements in treatments for DKD that slow progression and interventions for the prevention of DKD, yet DKD is a major, ever increasing, worldwide public health problem. The primary goals of the health care system need to be focused on the prevention and slowing of progression of DKD. The nephrology community has a dual task: to determine the best approach for both diagnosis and management. However, further education also is required across all health care providers (eg, endocrinologists, primary care physicians, nurse practitioners, physician assistants, and nurses) to understand the scope of the problem, implement interventions that prevent the development of DKD, ensure proper screening, understand how to diagnose, understand treatments if they do not want to refer, and understand when to refer to nephrology. It is a tall order, but a critical one.
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