Rationale and Strategies for Early Detection and Management of Diabetic Kidney Disease

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Diabetic kidney disease (DKD) occurs in 20% to 40% of patients with diabetes mellitus and is the leading cause of chronic kidney disease and end-stage renal disease in the United States. Despite the American Diabetes Association and the National Kidney Foundation advocating annual screening of diabetic patients, DKD remains underdiagnosed in the diabetic population. Early recognition of diabetic nephropathy by health care professionals is vital for proper management. The presence of microalbuminuria is particularly important as even low levels of dipstick-negative albuminuria indicate early disease long before a diminished glomerular filtration rate and are associated with an elevated cardiovascular disease risk. Like all forms of chronic kidney disease, DKD causes a progressive decline in renal function that, despite current treatment strategies, is largely irreversible. Many patients with DKD might be expected to develop end-stage renal disease, but many more patients will likely die of a cardiovascular event before renal replacement therapy is needed. Therefore, a renewed focus on cardiovascular risk factor reduction and a timely nephrology consultation with an emphasis on patient education is essential to proper DKD management.

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ACE = angiotensin-converting enzyme; ACR = albumin-to-creatinine ratio; ADA = American Diabetes Association; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; DKD = diabetic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; MDRD = Modification of Diet in Renal Disease; NKF = National Kidney Foundation; RAAS = renin-angiotensin-aldosterone system

The prevalence of both diabetes mellitus (DM) and chronic kidney disease (CKD) is steadily increasing in the United States. Current estimates suggest that 7% of the population (approximately 21 million people) have DM and that 13% of the population (approximately 26 million people) have CKD.[1,2] It may be argued that histologic findings of diabetic nephropathy, including glomerular basement membrane thickening and mesangial matrix expansion, are present in all patients with DM. However, diabetic kidney disease (DKD), defined as an elevated albumin excretion rate in a person with DM, occurs in 20% to 40% of patients with DM and is the leading cause of CKD and end-stage renal disease (ESRD) in the United States.[1,3] The increased prevalence of CKD is no doubt linked to the increased prevalence of DKD and DM, which is attributed largely to a dramatic increase in the obesity rate.[4]

In response to the growing prevalence of DKD and DM, which is increasingly recognized as an epidemic, the American Diabetes Association (ADA) and the National Kidney Foundation (NKF) have advocated annual screening for DKD in patients with DM by measuring their serum creatinine and albuminuria levels.[1,3] Despite these recommendations, DKD remains underdiagnosed in the DM population.[5-7] In a review of Medicare beneficiaries' records, proteinuria was measured in only 63% of patients with DM.[6] Furthermore, in a survey of more than 1000 primary care physicians, only 12% detected microalbuminuria in more than half of their patients with type 2 DM.[7]

Assessment of microalbuminuria is particularly important in diagnosing DKD because low levels of dipstick-negative albuminuria are an early clinical manifestation of diabetic nephropathy that may present several years before development of a diminished glomerular filtration rate (GFR). Spot urine samples have replaced the need for timed urine collections and can be used to easily identify patients with elevated albumin excretion rates by measuring the albumin-to-creatinine ratio (ACR). Once an elevated ACR has been detected, interventions should be initiated to slow the progression of DKD and possibly minimize the increased cardiovascular risk associated with DKD, a risk that exists even in the early stages of DKD.

Although DM has long been identified as a cardiovascular disease (CVD) risk equivalent, only recently has CKD been more widely recognized by primary care physicians in the United States as an independent risk factor for CVD and all-cause mortality.[8-11] In a study of more than 1 million ambulatory adult patients, the risk of a cardiovascular event and death due to any cause increased at every level of CKD below a GFR of 60 mL/min per 1.73 m^2, with a nearly 3.5-fold increased risk of a cardiovascular event and a 6-fold increased risk of death for those with a GFR of less than 15 mL/min per 1.73 m^2 (ie, CKD stage 5).[11] Furthermore, microalbuminuria alone has been associated with an increased risk of cardiovascular disease, both in patients with and without DM.[12-14] Therefore, in patients with DKD, the cardiovascular risks of DM and CKD are additive and increase as the kidney disease progresses.[15-17]

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TABLE 1. **Stages of Chronic Kidney Disease and Recommended Treatment**[a]

Stage	Description	GFR (mL/min per 1.73 m^2)	Treatment[b]
1	Kidney damage[c] with normal or elevated GFR	≥90	Manage comorbid conditions, slow progression,[d] reduce CVD risk
2	Kidney damage[c] with mildly reduced GFR	60-89	Estimate progression as follows: compare serial estimated GFRs using serum creatinine and MDRD calculation, track ACR
3	Moderately reduced GFR	30-59	Evaluate and manage complications as follows: (1) measure serum phosphorus level, consider use of phosphate binders and low-phosphorus diet; (2) measure vitamin D and parathyroid hormone levels, consider use of vitamin D supplementation; (3) measure hemoglobin, consider use of ESA
4	Severely reduced GFR	15-29	Prepare for kidney replacement therapy
5	Kidney failure (ESRD)	<15 or dialysis	Kidney replacement (if uremia present)

[a] ACR = albumin-to-creatinine ratio; CVD = cardiovascular disease; ESA = erythropoietic stimulating agent; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
[b] Includes treatments from preceding stages.
[c] Defined as abnormalities on pathologic, urine, blood, or imaging tests.
[d] Glycemic control plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
Data from *Ann Intern Med*.[9]

The current article presents results of a literature review conducted to clarify the rationale and strategies for early detection and management of DKD.

METHODS

The National Library of Medicine's PubMed database was used to conduct a review of literature published between January 1976 and June 2008. The following key terms were used in the search: *diabetes, kidney disease, microalbuminuria, glomerular filtration rate,* and *diabetic nephropathy*.

RESULTS

Overview of Renal Pathophysiology

The kidneys receive 25% of the cardiac output of blood. Although 20% of renal plasma flow (ie, approximately 180 L) is filtered through the glomerulus, only small amounts of protein can be detected in the urine.[18] Several plasma proteins are freely filtered, whereas others are prevented from crossing the glomerular filtration barrier, based on the proteins' molecular size and charge. The existence of several restrictive pores and of a glomerular charge barrier has been proposed to explain why the glomerulus is relatively impermeable to proteins of greater molecular weight (ie, >100 kDa) and to negatively charged proteins (eg, albumin).[18]

More recently, it has been suggested that, under normal conditions, a substantial amount of plasma protein, possibly at nephrotic levels, is filtered through the glomerulus, but proteinuria is prevented because of proximal tubule cell retrieval.[19] According to this idea, damage that disrupts the glomerular filtration barrier, or possibly the proximal tubular system, allows larger, negatively charged proteins that are normally contained within the serum to pass into the urine. The presence of such proteins, typically albumin, in the urine is an abnormal condition and is often one of the first signs of various forms of CKD, including DKD.

Chronic kidney disease is defined as kidney damage identified by proteinuria or by a GFR of less than 60 mL/min per 1.73 m^2 body surface area (with or without evidence of kidney damage) for 3 months or longer.[8,9] Table 1 shows the stages of CKD and the recommended treatments at each stage. In patients with DKD, the disease process begins with renal hypertrophy and hyperfiltration resulting from elevated renal plasma flow. In patients with type 1 DM and type 2 DM, hyperglycemia leads to increases in GFR of approximately 5% to 10%.[20-23] Although the mechanism is not completely understood, a correlation exists between glycosylated hemoglobin (HbA_{1c}) and GFR, and normalization of blood sugar levels has been shown to normalize GFR.[24,25] Other factors that influence hyperfiltration include increased ketone concentration, increased activity of the growth hormone/insulin-like growth factor system,[26] and disturbances in renal prostaglandins and the kallikrein-kinin system. In early-stage CKD, these abnormalities are frequently associated with enlarged kidneys.[27]

Hyperfiltration is typically followed by the loss of the negatively charged glomerular filtration barrier, allowing for negatively charged proteins, such as albumin, to pass through the glomerulus and into the urinary space. The presence of these proteins in the urinary space elevates urinary albumin excretion and produces microalbuminuria.[27] Microalbuminuria is defined as an albumin excretion rate between 30 and 300 mg per 24 hours, a range higher than the normal rate (<30 mg per 24 hours) but below the rate detectable by the standard urine dipstick method.[8] Overexcretion of albumin typically increases at a rate of 15% per year[28] and can result in macroalbuminuria (>300 mg per

24 hours) or even nephrotic-range proteinuria (>3.5 g per 24 hours).

In general, once macroalbuminuria (frank proteinuria) sets in, GFR begins to decline.[29] Progressive mesangial and interstitial capillary occlusion then occur, restricting the glomerular filtration surface and leading to a further decrease in GFR. Some proteins are reabsorbed by the renal tubules and accumulate in tubular epithelial cells. This accumulation induces the release of vasoactive and inflammatory cytokines, which damage the renal tubules and lead to tubular atrophy and interstitial fibrosis.[30] A negative feedback loop is thereby initiated, wherein increased proteinuria leads to increased tubulointerstitial injury and renal scarring, both of which further reduce GFR.[30]

Both hypertension and hyperglycemia are important in the development and progression of microalbuminuria and DKD. Table 2 presents a list of disorders associated with microalbuminuria. Several studies have shown that blood pressure elevations either precede or occur in conjunction with microalbuminuria in patients with both type 1 DM and type 2 DM.[29,31,32] Among patients with type 1 DM and DKD, those with increased urinary albumin excretion were found to be prehypertensive (120-139/80-89 mm Hg) at baseline, and their blood pressure and albuminuria levels increased in synch thereafter.[31,32] These elevations happened even though overt hypertension was not present before the onset of microalbuminuria. In patients with type 1 DM and DKD, blood pressure elevations before the onset of DM correlated with the future development of microalbuminuria.[33]

As previously mentioned, hyperglycemia can affect GFR and is necessary for the development of DKD. Likely mechanisms by which elevated glucose levels cause kidney damage include accumulation of advanced glycation end products, glucose-induced growth factor expression, and increased expression of inflammatory factors. However, hyperglycemia alone is insufficient to cause renal dysfunction.[30]

Most patients with DM never have clinically evident DKD, despite poor glycemic control. The absence of DKD in these patients suggests a genetic predisposition for DKD. The existence of such a predisposition is supported by studies showing an increased risk of nephropathy among people with a family history of the disorder.[34-36] Nevertheless, in susceptible individuals, hyperglycemia plays a crucial role in the progression of DKD from microalbuminuria to renal insufficiency and ESRD, as shown in type 1 DM by the Diabetes Control and Complications Trial[37] and in type 2 DM by the United Kingdom Prospective Diabetes Study.[38] Both these studies conclusively showed that the development and progression of DKD are strongly correlated with deficiencies in glucose control, verifying that glycemic control remains one of the cornerstones of treatment of DKD.

TABLE 2. **Disorders Associated With Microalbuminuria**

Elevated blood pressure
Dyslipidemia
Elevated fibrinogen and plasminogen activator inhibitor 1
Increased insulin resistance
Increased sodium disorders and related disorders
Increased transcapillary escape rate of albumin
Impaired basal endothelium-dependent vasorelaxation
Increased left ventricular volume
Diabetic retinopathy
Diabetic neuropathy
Peripheral vascular disease
Silent ischemic heart disease

Screening and Monitoring Techniques

The ADA recommends that both microalbuminuria and serum creatinine levels be assessed annually in patients with DM to screen for DKD.[3] For patients with type 1 DM, screening should begin 5 years after diagnosis because it takes at least that long for signs of nephropathy to develop. For patients with type 2 DM, screening should begin immediately at diagnosis because the precise onset of DM is often less clear, and the kidneys may have already sustained damage from years of undiagnosed hyperglycemia and/or hypertension.

After evidence of DKD has been detected, ongoing evaluations should be based on measurements of GFR.[3] However, in clinical practice, albuminuria is also typically measured to monitor disease progression and optimize therapy.

The following sections review the various methods used to measure GFR and albuminuria, focusing on the benefits and limitations of each.

Glomerular Filtration Rate. An index of functioning renal mass, GFR assessment is the most reliable method of detecting and monitoring renal impairment. Glomerular filtration rate can be measured directly or it can be estimated indirectly using the Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations. Simple measurement of serum creatinine is not recommended as an estimate of GFR because creatinine levels are greatly influenced by an individual's muscle mass, and thus simple measurements may overestimate or underestimate true GFR. Another reason that serum creatinine measurements may lead to an overestimation of GFR is that creatinine is cleared via secretion by the proximal tubule, and extrarenal excretion of creatinine is common in patients with more advanced CKD.[3,8,9]

Direct measurement of the fractional excretion of inulin, a fructose polysaccharide, is considered the criterion standard for GFR measurement. Inulin is inert, freely filtered at

the glomerulus, and neither secreted, reabsorbed, synthesized, nor metabolized by the kidneys. However, using inulin infusion to measure GFR is expensive, cumbersome, and not widely available. An alternative method for measuring GFR involves a single injection of a radioisotopic filtration marker, such as technetium Tc 99m DTPA (diethylenetriaminepentaacetic acid) or iothalamate I 125. This approach provides an accurate measure of GFR in cases of renal insufficiency, but it can overestimate GFR in healthy individuals and is also not widely available.[8,39]

The ADA and NKF recommend measuring the serum creatinine level and then using that value in either the MDRD or Cockcroft-Gault equations to estimate GFR.[1,3] Both these equations take into account variations in creatinine across age and sex, and the MDRD calculation also takes ethnicity into account.[40,41] The widely used MDRD calculation is considered more accurate than the Cockcroft-Gault equation for patients with CKD stage 2 or greater (GFR <90 mL/min per 1.73 m^2).[9] The MDRD equation was developed on the basis of direct GFR measurements and clearance of iothalamate ^{125}I in a study of 1628 patients of various ethnicities who had a variety of kidney disorders (6% had DM).[41] The MDRD was then validated in another group, consisting of more than 500 individuals.[41]

In general accuracy studies, more than 90% of GFR values estimated with the MDRD equation were within 30% of directly measured creatinine values, compared with 75% of values estimated with the Cockcroft-Gault equation.[8] Accuracy of estimates is improved if the clinical laboratory calibrates the creatinine measurement to the Cleveland Clinic's database, which includes approximately 9000 GFR measurements.[42] For this reason, many clinical laboratories are now undergoing the necessary steps to calibrate creatinine measurement.

Despite ADA and NKF recommendations, neither the MDRD calculation nor the Cockcroft-Gault equation has been validated for use in cases of diabetic nephropathy.[9] A recent accuracy study of patients with DM and microalbuminuria found that, although both the MDRD and Cockcroft-Gault equations correlated with directly measured GFR, both equations significantly underestimated the filtration rate, especially in patients with microalbuminuria.[43] The rate of renal decline was also significantly underestimated. The sensitivity of the equations to detect renal impairment was 72% for MDRD and 66% for Cockcroft-Gault. Furthermore, the use of these calculations led to accurate identification of CKD (as confirmed by a measured GFR <60 mL/min per 1.73 m^2) in only 51% (MDRD) and 66% (Cockcroft-Gault) of study participants.[43]

In a study of 169 patients with type 2 DM and macroalbuminuria, both equations underestimated GFR, although MDRD performed better than Cockcroft-Gault.[44] One study evaluated the equations by repeatedly measuring GFR with iothalamate for 10 years in 87 patients with type 2 DM and varying degrees of renal function: hyperfiltration, normal renal function, and CKD stage 2 or 3.[45] Both the MDRD and Cockcroft-Gault equations significantly underestimated GFR in patients with hyperfiltration and normal renal function. Nevertheless, in patients with CKD stage 2 or stage 3, GFR estimates made with MDRD closely matched iothalamate-determined GFR.[45]

The reason that the accuracy of the MDRD and Cockcroft-Gault equations is diminished in cases of DM is unknown. Creatinine clearance rate varies with age, sex, ethnicity, and body weight, and it is also affected by extremes of muscle mass and dietary intake. The NKF recommends that GFR be measured using direct clearance methods in patients with severe obesity, a population that includes many patients with type 2 DM but few with type 1 DM.[1] In patients with mild renal impairment (ie, CKD stage 1 or 2), the ability of the equations to estimate GFR is hampered by hypertrophy and hyperfiltration, which compensate for damaged nephrons[8] and may account for some of the observed inaccuracies.

An alternative approach being investigated is the measurement of cystatin C concentration as a surrogate for GFR. Cystatin C is a plasma protein that is freely filtered through the glomerulus and almost completely reabsorbed and catabolized by tubular cells. Several recent studies have examined the use of cystatin C concentration as an alternative method of estimating GFR. However, cystatin C is not yet used clinically because it is not widely available and is not currently recommended by either the ADA or the NKF.

Preliminary results suggest that cystatin C measurements may more accurately predict GFR than the MDRD or Cockcroft-Gault equations in patients with DM. In one study of 52 white patients with type 2 DM, the diagnostic accuracy of cystatin C measurements was 90% for identifying GFR at rates of less than 80 mL/min per 1.73 m^2, significantly greater than serum creatinine measurements alone (77%) or estimates made with the Cockcroft-Gault equation (85%).[46] A 4-year follow-up study of 30 Pima Indians with type 2 DM showed that GFR estimates based on cystatin C were numerically similar to GFR, as determined by iothalamate clearance, and that declining trends in renal function were correlated between the 2 measures (r=0.77).[47] By contrast, GFR estimates made with the MDRD or Cockcroft-Gault equation did not correlate well with iothalamate clearance (r<0.35).[47]

These provocative results await confirmation by larger studies. If the results are confirmed, cystatin C measurements may be used to arrive at more accurate assessments of CKD stage.

Albuminuria. Albuminuria can be assessed by timed collections, both overnight and 24-hour collections, and by spot urine tests used to measure ACR. Urine dipstick tests alone are not recommended for patients with DM because urinary protein levels vary with hydration and other factors, potentially leading to false-positive or false-negative results.[3]

The 24-hour timed collection of albuminuria remains the preferred method for the quantitative assessment of proteinuria; however, it is inconvenient, and over collection or under collection errors frequently result from missed or improperly timed samples. Overnight timed collections represent an alternative measure, but the shorter collection interval makes the sensitivity of overnight tests particularly vulnerable to under collection.[8]

The ADA and NKF now recommend measurement of ACR with a spot urine test to screen for diabetic nephropathy.[3] Several studies have shown clinical equivalency of ACR and 24-hour collections.[8,48-50] Both albumin and creatinine are highly soluble, and their dilution in urine is similar. Because creatinine excretion is generally constant, the ratio of albumin to creatinine accurately represents protein excretion during a 24-hour period.[8]

Several factors can increase urinary albumin over baseline values, leading to false-positive results, even when ACR is used as a measure. These factors include exercise within 24 hours of the urine test, urinary tract infection, fever, heart failure, marked hyperglycemia, marked hypertension, and protein intake. Furthermore, urinary albumin excretion has a notable intraindividual coefficient of variation, possibly as high as 40%.[51] To minimize this variability, first-morning-void urine samples are recommended. However, tests with positive results should be repeated, and a patient should not be considered to have elevated urinary albuminuria until 2 of 3 abnormal results have been obtained within a 3-month to 6-month time frame.[1,3]

Of note, a high-normal baseline level of albuminuria or a substantial increase in the level of albuminuria, even if still within the reference range, may signify future development of DKD.[52] For this reason, tests having such borderline negative results may require closer (eg, 6-month) follow-up, especially for patients at increased risk of DKD. For patients with documented renal impairment, annual evaluations of ACR should continue to assess disease progression and to monitor response to therapy (Table 1).

Rationale for Early Screening

Slowing Progression to ESRD. Diabetic kidney disease, like all forms of CKD, causes a progressive decline in renal function that may be retarded via several treatment strategies. Early recognition of DKD allows clinicians to optimize medical management and to educate patients about CKD so that patients can take measures to preserve residual renal function. Such measures may include weight loss, a low-protein diet, smoking cessation, and nephrotoxin avoidance.[53] In particular, use of nonsteroidal anti-inflammatory drugs should be discouraged.

Furthermore, early awareness of DKD may prompt clinicians to adjust dosages of antidiabetes agents and to consider more frequent diagnostic tests. Metformin hydrochloride, a widely prescribed antidiabetes agent, may generate lactic acidosis in patients with an estimated GFR of less than 60 mL/min per 1.73 m^2 and should be discontinued when the patient's serum creatinine level increases higher than 1.4 mg/dL in women and 1.5 mg/dL in men.[54] In addition, use of intravenous contrast dye and oral sodium phosphate solutions may precipitate contrast-induced nephropathy or acute phosphate nephropathy, respectively, in patients with impaired renal function.

Patient Preparation in Cases of ESRD. Despite aggressive measures, ESRD may be expected to develop in many patients with DKD, and ultimately some form of long-term renal replacement therapy will be needed. In the United States, the overwhelming majority of patients with ESRD undergo hemodialysis,[55] but preemptive living-related or living-unrelated donor kidney transplant is often feasible with appropriate planning.

Preparation for renal replacement therapy requires focused patient education and timely referrals to a nephrologist, vascular surgeon, and kidney transplant center. The success of such measures begins with early DKD recognition by the primary care physician.

Cardiovascular Risk Associated With CKD. Previous nephropathy screening guidelines for patients with DM focused on retarding progression to ESRD. However, in addition to being a risk factor for renal failure, CKD is now widely recognized as a major risk factor for CVD.[56] In a retrospective claims-based study of more than 1 million Medicare enrollees aged 65 years and older, the risk of cardiovascular events was significantly increased in those with either CKD or DM alone, but cardiovascular risk was greatest when both conditions were present (Figure).[57] These results are supported by prospective epidemiological studies that also showed an increased risk of CVD in patients with renal insufficiency.[10,11,58,59]

Elevated cardiovascular risk occurs early in the development of CKD, as demonstrated by studies showing that even low levels of albuminuria are predictive of CVD.[12-14] Using data collected from the Heart Outcomes Prevention Evaluation study, investigators found that the relative risk of myocardial infarction, stroke, and death due to CVD in patients with microalbuminuria was 1.97 among those with DM and 1.61 among those without.[13] Independent of diabe-

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