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Tactics to prevent or slow progression of CKD in patients with diabetes

Annual screening of urinary parameters, ongoing clinical vigilance, and proper medical therapy can help to keep declining renal function at bay.

PRACTICE RECOMMENDATIONS

› *Screen patients with diabetes annually for diabetic kidney disease with measurement of urinary albumin and the estimated glomerular filtration rate.* (B)

› *Optimize blood glucose and blood pressure control in patients with diabetes to prevent or delay progression to diabetic kidney disease.* (A)

› *Treat hypertensive patients with diabetes and stages 1 to 4 chronic kidney disease with an angiotensin-converting enzyme inhibitor or angiotensin II-receptor blocker as a first-line antihypertensive, absent contraindications.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Chronic kidney disease (CKD) is a significant comorbidity of diabetes mellitus. The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation defines CKD as the presence of kidney damage or decreased kidney function for ≥ 3 months. CKD caused by diabetes is called diabetic kidney disease (DKD), which is 1 of 3 principal microvascular complications of diabetes. DKD can progress to end-stage renal disease (ESRD), requiring kidney replacement therapy, and is the leading cause of CKD and ESRD in the United States.[1-3] Studies have also shown that, particularly in patients with diabetes, CKD considerably increases the risk of cardiovascular events, which often occur prior to ESRD.[1,4]

This article provides the latest recommendations for evaluating and managing DKD to help you prevent or slow its progression.

Defining and categorizing diabetic kidney disease

CKD is defined as persistently elevated excretion of urinary albumin (albuminuria) and decreased estimated glomerular filtration rate (eGFR), or as the presence of signs of progressive kidney damage.[5,6] DKD, also known as *diabetic nephropathy*, is CKD attributed to long-term diabetes. A patient's eGFR is the established basis for assignment to a stage (1, 2, 3a, 3b, 4, or 5) of CKD (**TABLE 1**[7]) and, along with the category of albuminuria (A1, A2, or A3), can indicate prognosis.

Taking its toll in diabetes

As many as 40% of patients with diabetes develop DKD.[8-10] Most studies of DKD have been conducted in patients with type 1 diabetes (T1D), because the time of clinical onset is typically known.

TABLE 1

How to establish prognosis in CKD based on estimated GFR and albuminuria[7]

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g (< 3 mg/mmol)	30-300 mg/g (3-30 mg/mmol)	> 300 mg/g (> 30 mg/mmol)
	G1	Normal to high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	< 15			

Color key: GREEN, low risk (note: if there are no other markers of kidney disease, there is no kidney disease); YELLOW, moderately increased risk; ORANGE, high risk; RED, very high risk.

CKD, chronic kidney disease; GFR, glomerular filtration rate (estimated).

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Type 1 diabetes. DKD usually occurs 10 to 15 years, or later, after the onset of diabetes.[6] As many as 30% of people with T1D have albuminuria approximately 15 years after onset of diabetes; almost one-half of those develop DKD.[5,11] After approximately 22.5 years without albuminuria, patients with T1D have approximately a 1% annual risk of DKD.[12]

Type 2 diabetes (T2D). DKD is often present at diagnosis, likely due to a delay in diagnosis and briefer clinical exposure, compared to T1D. Albuminuria has been reported in as many as 40% of patients with T2D approximately 10 years after onset of diabetes.[12,13]

Multiple risk factors with no standout "predictor"

Genetic susceptibility, ethnicity, glycemic control, smoking, blood pressure (BP), and the eGFR have been identified as risk factors for renal involvement in diabetes; obesity, oral contraceptives, and age can also contribute. Although each risk factor increases the risk of DKD, no single factor is adequately predictive. Moderately increased albuminuria, the earliest sign of DKD, is associated with progressive nephropathy.[12]

How great is the risk? From disease onset to proteinuria and from proteinuria to ESRD, the risk of DKD in T1D and T2D is similar. With appropriate treatment, albuminuria can regress, and the risk of ESRD can be < 20% at 10 years in T1D.[12] As in T1D, good glycemic control might result in regression of albuminuria in T2D.[14]

For unknown reasons, the degree of albuminuria can exist independent of the progression of DKD. Factors responsible for a progressive decline in eGFR in DKD without albuminuria are unknown.[12,15]

CONTINUED

As many as 30% of people with T1D have albuminuria approximately 15 years after onset of diabetes; almost one-half of those develop DKD.

Screen for potential comorbidities of DKD: For example, the risk of cardiovascular disease is significantly elevated in even moderately increased albuminuria.

Patient evaluation with an eye toward comorbidities

A comprehensive initial medical evaluation for DKD includes a review of microvascular complications; visits to specialists; lifestyle and behavior patterns (eg, diet, sleep, substance use, and social support); and medication adherence, adverse drug effects, and alternative medicines. Although DKD is often a clinical diagnosis, it can be ruled in by persistent albuminuria or decreased eGFR, or both, in established diabetes or diabetic retinopathy when other causes are unlikely (see "Recommended DKD screening protocol," below).

Screening for mental health conditions and barriers to self-management is also key.[6]

Comorbidities, of course, can complicate disease management in patients with diabetes.[16-20] Providers and patients therefore need to be aware of potential diabetic comorbidities. For example, DKD and even moderately increased albuminuria significantly increase the risk of cardiovascular disease (CVD).[12] Other possible comorbidities include (but are not limited to) nonalcoholic steatohepatitis, fracture, hearing impairment, cancer (eg, liver, pancreas, endometrium, colon, rectum, breast, and bladder), pancreatitis, hypogonadism, obstructive sleep apnea, periodontal disease, anxiety, depression, and eating disorders.[6]

Recommended DKD screening protocol

In all cases of T2D, in cases of T1D of ≥ 5 years' duration, and in patients with diabetes and comorbid hypertension, perform annual screening for albuminuria, an elevated creatinine level, and a decline in eGFR.

To confirm the diagnosis of DKD, at least 2 of 3 urine specimens must demonstrate an elevated urinary albumin:creatinine ratio (UACR) over a 3- to 6-month period.[21] Apart from renal damage, exercise within 24 hours before specimen collection, infection, fever, congestive heart failure, hyperglycemia, menstruation, and hypertension can elevate the UACR.[6]

Levels of the UACR are established as follows[22]:

- *Normal* UACR is defined as < 30 milligrams of albumin per gram of creatinine (expressed as "mg/g").
- *Increased* urinary albumin excretion is defined as ≥ 30 mg/g.
- *Moderately increased* albuminuria, a predictor of potential nephropathy, is the excretion of 30 to 300 mg/g.
- *Severely increased* albuminuria is excretion > 300 mg/g; it is often followed by a gradual decline in eGFR that, without treatment, eventually leads to ESRD.

The rate of decline in eGFR once albuminuria is severely increased is equivalent in T1D and T2D.[12] Without intervention, the time from severely increased albuminuria to ESRD in T1D and T2D averages approximately 6 or 7 years.

Clinical features

DKD is typically a clinical diagnosis seen in patients with longstanding diabetes, albuminuria, retinopathy, or a reduced eGFR in the absence of another primary cause of kidney damage. In patients with T1D and DKD, signs of retinopathy and neuropathy are almost always present at diagnosis, unless a diagnosis is made early in the course of diabetes.[12] Therefore, the presence of retinopathy suggests that diabetes is the likely cause of CKD.

The presence of microvascular disease in patients with T2D and DKD is less predictable.[12] In T2D patients who do not have retinopathy, consider causes of CKD other than DKD. Features suggesting that the cause of CKD is an underlying condition other than diabetes are rapidly increasing albuminuria or decreasing eGFR; urinary sediment comprising red blood cells or white blood cells; and nephrotic syndrome.[6]

As the prevalence of diabetes increases, it has become more common to diagnose DKD by eGFR *without* albuminuria—underscoring the importance of routine monitoring of eGFR in patients with diabetes.[6]

Sources of expert guidance. The Chronic Kidney Disease Epidemiology Collaboration equation[23] is preferred for calculating eGFR from serum creatinine: An eGFR < 60 mL/min/1.73 m^2 is considered abnormal.[3,12] At these rates, the prevalence of com-

TABLE 2
Screening for mineral and bone disorder in CKD[52]

	Analyte			
STAGE OF CKD (BASED ON THE eGFR[a])	**Calcium and potassium**	**Parathyroid hormone**	**Alkaline phosphatase**	**25-hydroxyvitamin D**
Stage 1 (≥ 90)	Every 6-12 mo	Once, then repeated as necessary based on level and progression of CKD	Every 12 mo	Once, then repeated as necessary based on level and treatment
Stage 2 (60-89)				
Stage 3 (30-59)				
Stage 4 (15-29)	Every 3-6 mo	Every 6-12 mo		
Stage 5 (< 15)	Every 1-3 mo	Every 3-6 mo		

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate
[a] mL/min/1.73 m^2.

plications related to CKD rises and screening for complications becomes necessary.

A more comprehensive classification of the stages of CKD, incorporating albuminuria and progression of CKD, has been recommended by Kidney Disease: Improving Global Outcomes (KDIGO).[7] Because eGFR and excretion of albumin vary, abnormal test results need to be verified over time to stage the degree of CKD.[3,12] Kidney damage often manifests as albuminuria, but also as hematuria, other types of abnormal urinary sediment, radiographic abnormalities, and other abnormal presentations.

Management

Nutritional factors

Excessive protein intake has been shown to increase albuminuria, worsen renal function, and increase CVD mortality in DKD.[24-26] Therefore, daily dietary protein intake of 0.8 g/kg body weight is recommended for patients who are not on dialysis.[3] Patients on dialysis might require higher protein intake to preserve muscle mass caused by protein-energy wasting, which is common in dialysis patients.[6]

Low sodium intake in CKD patients has been shown to decrease BP and thus slow the progression of renal disease and lower the risk of CVD. The recommended dietary sodium intake in CKD patients is 1500-3000 mg/d.[3]

Low potassium intake. Hyperkalemia is a serious complication of CKD. A low-potassium diet is recommended in ESRD patients who have a potassium level > 5.5 mEq/L.[6]

Blood pressure

Preventing and treating hypertension is critical to slowing the progression of CKD and reducing cardiovascular risk. BP should be measured at every clinic visit. Aside from lifestyle changes, medication might be needed to reach target BP.

The American Diabetes Association recommends a BP goal of ≤ 140/90 mm Hg for hypertensive patients with diabetes, although they do state that a lower BP target (≤ 130/80 mm Hg) might be more appropriate for patients with DKD.[27]

The American College of Cardiology recommends that hypertensive patients with CKD have a BP target of ≤ 130/80 mm Hg.[28]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have renoprotective benefits. These agents are recommended as first-line medications for patients with diabetes, hypertension, and an eGFR < 60 mL/min/1.73 m^2 and a UACR > 300 mg/g.[29-31] Evidence also supports their use when the UACR is 30 to 299 mg/g.

Studies have shown that, in patients with DKD, ACE inhibitors and ARBs can slow the progression of renal disease.[29,30,32] There is no difference between ACE inhibitors and ARBs in their effectiveness for preventing progression of DKD.[6] There is no added benefit in combining an ACE inhibitor and an

ARB[33]; notably, combination ACE inhibitor and ARB therapy can increase the risk of adverse events, such as hyperkalemia and acute kidney injury, especially in patients with DKD.[33]

There is no evidence for starting an ACE inhibitor or ARB to prevent CKD in patients with diabetes who are not hypertensive.[5]

ACE inhibitors and ARBs should be used with caution in women of childbearing age, who should use a reliable form of contraception if taking one of these drugs.

Diuretics. Thiazide-type and loop diuretics might potentiate the positive effects of ACE inhibitors and ARBs. KDOQI guidelines recommend that, in patients who require a second agent to control BP, a diuretic should be considered in combination with an ACE inhibitor or an ARB.[20] A loop diuretic is preferred if the eGFR is < 30 mL/min/1.73 m^2.

Nondihydropyridine calcium-channel blockers (CCBs), such as diltiazem and verapamil, have been shown to be more effective then dihydrophyridine CCBs, such as amlodipine and nifedipine, in slowing the progression of renal disease because of their antiproteinuric effects. However, the antiproteinuric effects of nondihydropyridine CCBs are not as strong as those of ACE inhibitors or ARBs, and these drugs do not appear to potentiate the effects of an ACE inhibitor or ARB when used in combination.[20]

Nondihydropyridine CCBs might be a reasonable alternative in patients who cannot tolerate an ACE inhibitor or an ARB.

Mineralocorticoid receptor antagonists in combination with an ACE inhibitor or ARB have been demonstrated to reduce albuminuria in short-term studies.[34,35]

Confirmation of suspected DKD requires an elevated albumin:creatinine ratio in at least 2 of 3 urine specimens over a 3- to 6-month period.

Glycemic levels

Studies conducted in patients with T1D, and others in patients with T2D, have shown that tight glycemic control can delay the onset and slow the progression of albuminuria and a decline in the eGFR.[10,36-39] The target glycated hemoglobin (A1C) should be < 7% to prevent or slow progression of DKD.[40] However, patients with DKD have an increased risk of hypoglycemic events and increased mortality with more intensive glycemic control.[40,41] Given those findings, some patients with DKD and significant comorbidities, ESRD, or limited life expectancy might need to have an A1C target set at 8%.[6,42]

Adjustments to antidiabetes medications in DKD

In patients with stages 3 to 5 DKD, several common antidiabetic medications might need to be adjusted or discontinued because they decrease creatinine clearance.

First-generation sulfonylureas should be avoided in DKD. Glipizide and gliclazide are preferred among second-generation sulfonylureas because they do not increase the risk of hypoglycemia in DKD patients, although patients taking these medications still require close monitoring of their blood glucose level.[20]

Metformin. In 2016, recommendations changed for the use of metformin in patients with DKD: The eGFR, not the serum creatinine level, should guide treatment.[43] Metformin can be used safely in patients with (1) an eGFR of < 60 mL/min/1.73 m^2 and (2) an eGFR of 30 mL/min/1.73 m^2 with close monitoring. Metformin should not be initiated if the eGFR is < 45 mL/min/1.73 m^2.[43]

Antidiabetes medications with direct effect on the kidney

Several antidiabetes medications have a direct effect on the kidney apart from their effect on the blood glucose level.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce albuminuria and slow the decrease of eGFR independent of glycemic control. In addition, SGLT2 inhibitors have also been shown to have cardiovascular benefits in patients with DKD.[44,45]

Glucagon-like peptide 1 (GLP-1) receptor agonists have been shown to delay and decrease the progression of DKD.[46-48] Also, similar to what is seen with SGLT2 inhibitors, GLP-1 agonists have demonstrable cardiovascular benefit in patients with DKD.[46,48]

Dyslipidemia and DKD

Because the risk of CVD is increased in patients with DKD, addressing other modifiable risk factors, including dyslipidemia, is recom-

mended in these patients. Patients with diabetes and stages 1 to 4 DKD should be treated with a high-intensity statin or a combination of a statin and ezetimibe.[49,50]

If a patient is taking a statin and starting dialysis, it's important to discuss with him or her whether to continue the statin, based on perceived benefits and risks. It is not recommended that statins be initiated in patients on dialysis unless there is a specific cardiovascular indication for doing so. Risk reduction with a statin has been shown to be significantly less in dialysis patients than in patients who are not being treated with dialysis.[49]

Complications of CKD

Anemia is a common complication of CKD. KDIGO recommends measuring the hemoglobin concentration annually in DKD stage 3 patients without anemia; at least every 6 months in stage 4 patients; and at least every 3 months in stage 5. DKD patients with anemia should have additional laboratory testing: the absolute reticulocyte count, serum ferritin, serum transferrin saturation, vitamin B12, and folate.[51]

Mineral and bone disorder should be screened for in patients with DKD. **TABLE 2**[52] outlines when clinical laboratory tests should be ordered to assess for mineral bone disease.

When to refer to a nephrologist

Refer patients with stage 4 or 5 CKD (eGFR, ≤ 30 mL/min/1.73 m^2) to a nephrologist for discussion of kidney replacement therapy.[6] Patients with stage 3a CKD and severely increased albuminuria or with stage 3b CKD and moderately or severely increased albuminuria should also be referred to a nephrologist for intervention to delay disease progression.

Identifying the need for early referral to a nephrologist has been shown to reduce the cost, and improve the quality, of care.[53] Other indications for earlier referral include uncertainty about the etiology of renal disease, persistent or severe albuminuria, persistent hematuria, a rapid decline in eGFR, and acute kidney injury. Additionally, referral at an earlier stage of DKD might be needed to assist with complications associated with DKD, such as anemia, secondary hyperparathyroidism, mineral and bone disorder, resistant hypertension, fluid overload, and electrolyte disturbances.[6] JFP

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Tight glycemic control in T1D and T2D can delay the onset, and slow the progression, of albuminuria and a decline in the eGFR.

Nutritional control is important in DKD: A low-sodium diet can slow progression of DKD, and a low-potassium diet can prevent hyperkalemia in end-stage renal disease.

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