Screening, Monitoring, Prevention, and Treatment Strategies for Chronic Kidney Disease in Patients with Type 2 Diabetes

Sam Dagogo-Jack, MD, DSc

Diabetes is a major risk factor for chronic kidney disease (CKD), and an estimated 20–40% of people with diabetes have evidence of CKD (109,201–205). In people with type 1 diabetes, CKD usually develops ≥10 years after diagnosis of diabetes. Because the exact time of onset of type 2 diabetes is often unclear and many patients may have had the condition for several years before diagnosis, CKD can manifest at diagnosis of type 2 diabetes. There is even evidence that CKD can occur in people with prediabetes (206,207).

CKD does not remit spontaneously; its severity gradually progresses to end-stage renal disease (ESRD) in the absence of intervention. Besides being the leading cause of ESRD, there is a markedly increased burden of cardiovascular morbidity, premature mortality, and health care expenditure associated with CKD (205,208–210). CKD is clinically silent at its early stages, and individuals with even advanced stages may lack pathognomonic symptoms. In some patients, polyuria and polydipsia may be clues to impaired urine concentration from CKD; however, such symptoms lack sensitivity and specificity and are often ignored. Complaints of weakness and lassitude, particularly in the setting of anemia, are other nonspecific symptoms associated with advanced CKD.

The natural history of CKD in patients with type 1 diabetes is characterized by the presence of diabetic retinopathy, albuminuria with an inactive urinary sediment, and progressive decline in estimated glomerular filtration rate (eGFR). People with type 2 diabetes exhibit these same features, with or without the presence of retinopathy (211). Furthermore, many people with type 1 or type 2 diabetes can have reduced eGFR without albuminuria, a pattern that is being increasingly observed (211,212). The corollary is that a person with diabetes with an active urinary sediment (showing cellular casts, red blood cells, or white blood cells), rapidly worsening or massive albuminuria, or sharp decline in eGFR requires evaluation by a nephrologist for alternative or atypical causes of kidney disease.

Unfortunately, owing to its largely asymptomatic nature, most patients in the early stages of CKD are not aware that they have the disease (202,212–214). Even among patients with severely reduced kidney function (glomerular filtration rate [GFR] <45 mL/min/1.73 m^2), ~50% may not be aware that they have CKD (212,213). Given the high morbidity and mortality risks associated with CKD, the enormous costs of managing ESRD, and the treacherously asymptomatic nature of the disease, increased surveillance through regular, targeted screening of at-risk individuals is the dominant strategy for containing the scourge of CKD.

Screening for CKD in People with Diabetes

The current approach to screening individuals for the presence of CKD is based on documentation of elevated urinary albumin excretion (albuminuria) and decline in eGFR (**Table 1**) (109,168,215–217).

Albuminuria

Glomerular hyperfiltration is a cardinal manifestation of incipient nephropathy, and measurement of albumin excretion in a 24-hour urine collection provides significant insight into renal health. Albumin excretion rates of 30–300 mg/24 hours (historically called microalbuminuria) indicate incipient nephropathy and predict progression to higher-grade albuminuria (>300 mg/24 hours, historically called macroalbuminuria) and decline in GFR in the ensuing several years (218,219). Because of challenges in obtaining adequate 24-hour urine collections from patients, the albumin-to-creatinine ratio (ACR) in random spot urine samples has been validated as a convenient and reliable alternative approach (168,220). The simple measurement of a spot urine albumin level alone by dipstick or other methods is inadequate for assessing renal

TABLE 1 Screening for CKD in Patients with Diabetes

Test	Frequency	Values
Albuminuria test in spot urine specimen, mg/g creatinine	▸ Type 1 diabetes: annually from 5 years after diagnosis ▸ Type 2 diabetes: annually from time of diagnosis ▸ More frequently in patients with values >300 mg/g to assess progression and response to treatment	▸ Normal: <30 ▸ Moderately increased: 30–300 ▸ Severely increased: >300
eGFR, mL/min/1.73 m^2	▸ Type 1 diabetes: annually from 5 years after diagnosis ▸ Type 2 diabetes: annually from time of diagnosis ▸ More frequently in patients with eGFR <60 mL/min/1.73 m^2, to assess progression and response to treatment	▸ Normal or high: ≥90 ▸ Mildly decreased: 60–89 ▸ Mildly to moderately decreased: 45–59 ▸ Moderately to severely decreased: 30–44 ▸ Severely decreased: 15–29 ▸ Kidney failure: <15

function, as such measurements are prone to false-negative and false-positive errors resulting from variations in urine concentration and hydration status (168,221). Therefore, a more appropriate approach is simultaneous measurement of albumin and creatinine concentrations in spot urine and derivation of the ACR (168).

A normal value for urinary ACR is <30 mg/g creatinine. Values of ≥30 mg/g indicate elevated ACR (**Table 1**).

The interpretation of ACR requires several careful considerations. First, there is a gradation of renal and cardiovascular risk even within the normal range of urinary ACR; therefore, a patient's full clinical profile must be considered before declaring low ACR values as evidence of normal organ function. Second, because of a high (≥20%) biological variability between urinary ACR measurements, it is recommended that the diagnosis of elevated albuminuria be based on positive results in at least two of three urine specimens obtained within 3–6 months (109,168,201,220,221). Note that urinary ACR has a continuous distribution of values; thus, differences within the normal and abnormal ranges are associated with renal and cardiovascular outcomes (168,203,209,210). Urine albumin excretion can be affected by recent exercise, febrile illness, infection, heart failure (HF), severe hyperglycemia, uncontrolled severe hypertension, and contamination with menstrual flow, among other factors (**Table 2**). Therefore, care must be taken to avoid spurious results, and the test should be repeated to confirm doubtful values.

TABLE 2 Factors That Increase Urinary Albumin Excretion

- Exercise
- Febrile illness
- Urinary tract infection
- Hematuria
- Menstruation
- HF
- Severe hyperglycemia
- Severe hypertension

eGFR

eGFR is calculated automatically by most laboratories from the serum creatinine level, using well-validated formulas (109,168,211,216,217). Traditionally, the GFR estimation equations have applied a correction factor based on self-described race/ethnicity, but that step is currently under re-evaluation. Values of eGFR ≥90 mL/min/1.73 m^2 are generally normal or high, and decreasing values indicate gradations of decline in kidney function (**Table 1**). However, because of physiological age-related decline in renal function, the eGFR threshold for diagnosis of CKD in older individuals is somewhat imprecise (168). Urinary ACR and eGFR values are useful metrics for the screening, diagnosis, staging, prognostication, and management of CKD (109,168,201,202,211,216,217) (**Table 1**).

Current CKD screening guidelines recommend measurement of spot urinary ACR and eGFR at least annually in patients with type 1 diabetes of ≥5 years' duration and in all patients with type 2 diabetes from the time of diagnosis (168,211,216,217) (**Table 1**). Patients with diabetes whose tests reveal a urinary ACR >300 mg/g and/or an eGFR in the range of 30–60 mL/min/1.73 m^2 should be monitored more frequently to gauge the adequacy of treatment interventions (168).

Approach to Prevention and Treatment of CKD in People with Diabetes

Lifestyle Modification

Adoption of healthy lifestyle habits should be promoted in people with diabetes and CKD. In particular, smoking cessation should be encouraged and supported with proven medical interventions such as prescription of bupropion or varenicline and/or cognitive behavioral counseling (168,216,217,222). Current dietary recommendations for adjunctive CKD management have become less stringent than in the past. The dietary protein intake recommended for people with CKD not yet requiring dialysis treatment is ~0.8 g/kg body weight/day, similar to the daily allowance for healthy people. Dietary protein intake at this level has been shown to delay eGFR decline compared with higher levels of intake (168). Indeed, dietary protein intake >1.3 g/kg/day has been associated with worsening albuminuria and accelerated loss of kidney function (168,223). However, reducing dietary protein intake to <0.8 g/kg/day does not improve renal function or decline in eGFR and is not recommended (223,224). Once dialysis treatment has been initiated, it is prudent to recommend higher levels of dietary protein intake to guard against likely malnutrition from the hypercatabolic milieu of advanced CKD (223,224). Dietary sodium restriction to <2,300 mg/day may improve blood pressure control and decrease cardiovascular risk (225). On an individual basis, restriction of dietary potassium may be appropriate; patients with significant reduction in eGFR may have impaired urinary excretion of potassium with consequent risk of hyperkalemia (**Table 3**) (223,226).

TABLE 3 Approach to Prevention and Treatment of CKD in Diabetes

- Lifestyle modification
  - Appropriate dietary protein intake
  - Sodium restriction
  - Potassium management
- Optimization of blood pressure control
  - Preferential use of angiotensin system inhibitors
  - Consideration of MR antagonists
- Optimization of glycemic control
- Specific use of SGLT2 inhibitors
- Consideration of GLP-1 receptor agonists

Optimization of Blood Pressure and Glycemic Control

There is abundant evidence from randomized controlled trials (RCTs) that control of blood pressure and blood glucose can reduce the risk of CKD and delay its progression in people with diabetes (218,227–230).

Blood Pressure Control

Hypertension is a leading cause of CKD, a risk that can be mitigated by effective antihypertensive therapy (227,228,231–234). Reduction of blood pressure decreases the risk of developing albuminuria, in addition to conferring cardioprotective benefits (227,228,231–235). In patients with type 1 or type 2 diabetes who have already developed CKD (eGFR <60 mL/min/1.73 m^2 and urinary ACR ≥300 mg/g), treatment with ACE inhibitor or angiotensin receptor blocker (ARB) therapy delays the worsening of decline in renal function and progression to ESRD (3,168,236). The generally recommended target blood pressure level for cardiorenal protection in people with diabetes is <140/90 mmHg (168). Lower blood pressure targets (e.g., <130/80 mmHg) may be appropriate to further reduce the risks of cardiovascular disease (CVD) and CKD progression in selected patients (e.g., those with albuminuria ≥300 mg/g) (168). Based on their now well-documented cardiorenal protective benefits, ACE inhibitors and ARBs are the recommended first-line agents for blood pressure control in nonpregnant patients with diabetes, hypertension, an eGFR <60 mL/min/1.73 m^2, and urinary ACR ≥300 mg/g (168,216,217).

Combination therapy with an ACE inhibitor and an ARB has no benefits on CVD or CKD outcomes, may increase adverse events, and is therefore unwarranted (237). The fairly widespread clinical practice of prescribing an ACE inhibitor or ARB for normotensive patients with elevated albuminuria also is not evidence-based, as the benefit of that approach on renal outcomes has yet to be demonstrated in RCTs (168). Currently, treatment with an ACE inhibitor or ARB is not recommended for the primary prevention of CKD in normotensive patients with diabetes who have normal urinary ACR (<30 mg/g) and a normal eGFR (168).

The addition of a mineralocorticoid receptor (MR) antagonist (spironolactone, eplerenone, or finerenone) to background antihypertensive medication, including an ACE inhibitor or ARB, is an established clinical strategy for improving blood pressure control in patients with resistant hypertension (168,238). Preliminary studies have suggested that combination drug regimens that include an MR antagonist may reduce the risks of albuminuria and CVD (239). The findings of a recent, large RCT support the long-term beneficial effects of finerenone, an investigational nonsteroidal MR antagonist, on CKD and CVD outcomes in people with type 2 diabetes (9). Notably, the participants were already receiving treatment with the maximum recommended (or tolerated) dose of an ACE inhibitor or ARB. During a median follow-up of 2.6 years, treatment with finerenone, compared to placebo, resulted in an 18% reduction in the occurrence of the primary outcome (≥40% decline in eGFR from baseline or death from renal causes) and a 14% reduction in a secondary outcome (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF) (9). Thus, patients with CKD and type 2 diabetes already receiving angiotensin system blocking agents experienced significant reductions in CKD progression, major CVD events, and HF after the addition of finerenone to the treatment regimen.

Glycemic Control

Care must be taken in the selection of medications and doses for lowering blood glucose in people with CKD to avoid increased risks of hypoglycemia, increased toxicity from drug accumulation, or loss of efficacy with declining eGFR that may occur with some drugs (240). The doses of certain drugs, including insulin, sulfonylureas, meglitinides, and some dipeptidyl peptidase 4 inhibitors, may require adjustments in patients with CKD (as indicated by serum creatinine or eGFR <60 mL/min/1.73 m^2 [201]).

The use of metformin, the most widely recommended initial drug for people with type 2 diabetes, has had restrictions based on kidney function, principally because of the risk of rare lactic acidosis (241). The 2016 U.S. Food and Drug Administration (FDA) revised guidance for the use of metformin in CKD stipulates that eGFR instead of serum creatinine be used to determine and monitor the safety of metformin therapy (242). According to the FDA guidance, metformin should not be initiated in patients with an eGFR <45 mL/min/1.73 m^2 and is contraindicated in patients whose eGFR decreases to <30 mL/min/1.73 m^2 while taking metformin. Metformin should be stopped temporarily shortly before or on the day of exposure to iodinated contrast media in patients with an eGFR of 30–60 mL/min/1.73 m^2 (242). Thus, metformin remains the first-line treatment for all patients with type 2 diabetes, including those with CKD, once the rubrics in the FDA guidance have been considered (242,243).

Achievement and maintenance of an A1C target of <7% has been shown in landmark clinical trials to reduce the risk of development or progression of CKD in people with type 1 or type 2 diabetes (45,46,49,228,229,244,245). In the Diabetes Control and Complications Trial (DCCT) (244), during a mean follow-up period of 6.5 years, patients with type 1 diabetes on intensive treatment (mean A1C ~7%) versus conventional treatment (mean A1C ~9%) experienced risk reductions of 35% for the development of albuminuria (30–299 mg/day) and 56% for albuminuria (>300 mg/day). Combined data from the DCCT and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) cohort (median follow-up 22 years) showed that intensive glycemic control during the DCCT was associated with a 50% risk reduction in the incidence of CKD (GFR <60 mL/min/1.73 m^2) and ESRD, despite convergence of the mean A1C to ~8% in the two treatment groups (228,229). In the UK Prospective Diabetes Study (UKPDS) (45), patients with newly diagnosed type 2 diabetes who were assigned to intensive treatment (median A1C ~7%) versus conventional treatment (median A1C 7.9%) decreased their risk of albuminuria and had a 67% risk reduction in doubling of plasma creatinine level (45). As was observed post-DCCT, the 0.9% difference in A1C

between groups during the UKPDS disappeared after 1 year of additional follow-up. Despite the glycemic convergence, 10-year post-UKPDS follow-up data showed persistence of the benefits of intensive glucose control on renal and other microvascular endpoints (24% risk reduction) (46).

These results from the UKPDS follow-up and the DCCT/EDIC studies support the concept of "metabolic memory" or "legacy effect" and emphasize the importance of early intervention (245). In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study (49), patients with type 2 diabetes who achieved a mean A1C of 6.5% showed a 21% relative reduction in the development of new or worsening nephropathy compared to a control group (mean A1C 7.3%) during a median follow-up period of 5 years. Note, however, that intensive glycemic control may be associated with a modest initial decline in GFR (possibly resulting from amelioration of hyperfiltration), as was observed in the DCCT. Reassuringly, after 10 years of follow-up (the EDIC phase), intensive glucose control was associated with a slower decline in GFR and higher mean eGFR compared with conventional therapy (228,229). Underscoring the importance of glycemic control, the DCCT investigators reported that the effect of improved glycemic control on GFR remained significant after adjustments for blood pressure, BMI, and the use of antihypertensive agents, including inhibitors of the renin-angiotensin-aldosterone system, and was fully attenuated after adjustment for A1C (228,229).

Together, the results from these landmark clinical trials demonstrate that achieving A1C levels of ~7% early in the course of diabetes is specifically associated with decreased risk of diabetic nephropathy (45,46,49,228,229,244,245). Furthermore, even in the setting of preexisting nephropathy, improved glycemic control can slow the rate of progression of CKD (49,228,229). Intensive glycemic control with the goal of achieving near-normoglycemia has been shown in other large prospective randomized studies to delay the onset and progression of albuminuria and CKD in patients with diabetes (246,247). Despite the demonstrated value of intensive glycemic control, it should be cautioned that the presence of CKD can increase the risk of hypoglycemia, with deleterious consequences including potentially fatal cardiac arrhythmias (240,248,249). Thus, the target A1C should be individualized in patients with CKD, particularly those who harbor cardiovascular and other comorbidities (168).

Role of Antidiabetic Agents with Renoprotective Effects

Beyond general glycemic control and optimization of blood pressure, recent evidence supports the specific benefits of certain antidiabetic medications on renal health. The strongest such evidence pertains to drugs from the sodium–glucose cotransporter 2 (SGLT2) inhibitor class, but there is also limited evidence for the glucagon-like peptide 1 (GLP-1) receptor agonists.

SGLT2 Inhibitors

SGLT2 inhibitors improve blood pressure control by blocking renal tubular glucose reabsorption and inducing glycosuria, but these drugs also block renal sodium reabsorption and decrease body weight, blood pressure, and intraglomerular pressure (250,251). The clinically measurable renal effects of SGLT2 inhibitors include a transient decrease in GFR followed by sustained slowing of decline in GFR along with reduction of albuminuria (5,6,161,250,251). The beneficial effects on albumin excretion and GFR decline do not seem to be related to the glycemic effect of SGLT2 inhibitors, and their exact underlying mechanisms are under investigation. Some proposed mechanisms/mediators include effects of SGLT2 inhibitors on redox state, angiotensinogen expression, inflammation, and the sodium hydrogen exchanger in the kidney, among others (252–255). Significant reductions in various measures of kidney outcomes, including albuminuria, doubling of serum creatinine, decline in eGFR, and occurrence of ESRD or renal death have been observed when comparing SGLT2 inhibitors to placebo in patients with diabetes (5,6,156,161,251,256), including those with preexisting severe CKD or HF (53,257).

The currently approved SGLT2 inhibitors have different cutoff eGFR levels for dosing considerations based on the glycemic efficacy demonstrated in the populations studied in clinical trials (**Table 4**) (258–261). However, it is likely that the eGFR cutoffs might change after ongoing regulatory review of candidate SGLT2 inhibitor drugs

TABLE 4 FDA-Approved SGLT2 Inhibitors and GFR Considerations for Dose Selection for Glycemic Control

eGFR, mL/min/1.73 m^2	Canagliflozin (258)	Dapagliflozin (259)	Empagliflozin (260)	Ertugliflozin (261)
≥60	100 mg once daily with titration to 300 mg once daily	5 mg once daily with titration to 10 mg once daily	10 mg once daily with titration to 25 mg once daily	5 mg once daily with titration to 15 mg once daily
45–60	100 mg once daily	5 mg once daily with titration to 10 mg once daily	10 mg once daily with titration to 25 mg once daily	
30 to <45	▸ 100 mg once daily ▸ Approved down to an eGFR of 30 (Initiation is not recommended; however, patients with albuminuria >300 mg/day may continue.)	Limited glycemic benefit but no dose adjustment needed to decrease the risk of cardiovascular death or hospitalization for heart failure in patients with diabetes down to an eGFR of 30	▸ Do not initiate ▸ Discontinue if GFR falls into this range.	▸ Do not use in patients with an eGFR <30 ▸ Initiation is not recommended in patients with an eGFR of 30–60 ▸ Continued use is not recommended in patients with an eGFR persistently between 30 and <60

specifically for the treatment of patients with CKD. SGLT2 inhibitors are generally well-tolerated oral drugs, and their most notable adverse effects are an increased risk of genital mycotic infection, hypovolemic symptoms, and rare ketoacidosis (5,6,161,251). To minimize the risk of ketoacidosis, it is prudent for patients to withhold SGLT2 inhibitors during periods of prolonged fasting or critical illness or perioperatively. Patients with hypovolemia may benefit from a reduction in the doses of concomitant diuretic medications (217).

GLP-1 Receptor Agonists

In addition to the SGLT2 inhibitors, analysis of cardiovascular outcomes trials of GLP-1 receptor agonists has shown evidence of kidney benefits when assessed as secondary outcomes (7,51). Significant decreases in the composite measures of urinary ACR, new or worsening nephropathy, doubling of serum creatinine, ESRD, or death from ESRD have been reported for GLP-1 receptor agonists (liraglutide: 22% reduction vs. placebo, semaglutide: 36% reduction vs. placebo) (7,51). The GLP-1 receptor agonists significantly reduce the risk of atherosclerotic cardiovascular events and also have direct effects on the kidney that may explain the improved renal outcomes (262). However, pending the results of ongoing evaluations dedicated to patients with CKD, the weight of available evidence accords priority to SGLT2 inhibitors in the overall strategy of preventing progression of CKD in people with type 2 diabetes (**Table 3**) (168,262,263). Thus, consideration of GLP-1 receptor agonists would be most appropriate in patients with suboptimal glycemic control despite the use of metformin and an SGLT2 inhibitor or who cannot tolerate those medications. Based on current evidence, a long-acting GLP-1 receptor agonist is recommended, and the treatment should be initiated at the lowest dose and titrated slowly to minimize gastrointestinal side effects (217).

Monitoring CKD in People with Diabetes and Referring Patients to Nephrologist

Patients with CKD should undergo regular clinical surveillance and measurement of urinary ACR and eGFR to monitor disease progression, adverse drug effects, and other complications. Serum creatinine and potassium levels should be monitored periodically in patients treated with an ACE inhibitor, ARB, or diuretic, as alterations in creatinine and potassium levels may warrant treatment modification (168,216,217). It is prudent practice to document and assess the effects of exposure to nephrotoxins (e.g., nonsteroidal anti-inflammatory drugs, aminoglycosides, and iodinated contrasts) as a possible explanation for any unexpected decline in kidney function parameters.

Modest elevations in serum creatinine can occur with exposure to ACE inhibitors and ARBs that should not cause undue clinical concern or necessitate abrupt discontinuation of life-saving treatment (168,264). Increases in serum creatinine up to 30% above baseline values after intensification of blood pressure control with these agents have been shown to be clinically benign and not associated with any increase in biomarkers of acute kidney injury (AKI) or risks of CKD progression or mortality (264,265). Thus, after careful evaluation and elimination of other factors, an increase ≤30% in serum creatinine in an otherwise stable and well-hydrated patient treated with an ACE inhibitor or ARB does warrant cessation of therapy (168,264,265).

The typical findings in diabetes-related CKD include long duration of diabetes (usually ≥10 years), presence of diabetic retinopathy, albuminuria, inactive urinary sediment, and gradual decline in eGFR (168,201,216,217). Patients who present with atypical findings, massive proteinuria, a rapidly declining eGFR, or other unusual features would benefit from referral to a nephrologist (168,216,217). Referral is also prudent whenever there is uncertainty about the diagnosis or etiology of kidney disease in a patient with diabetes. Other candidates for management in consultation with a nephrologist include patients with complex comorbidities (e.g., anemia of CKD, secondary hyperparathyroidism, and metabolic bone disease) and those with advanced CKD (eGFR <30 mL/min/1.73 m^2), who would require planning for renal replacement therapy for ESRD (**Table 5**) (109,168,201,216,217).

TABLE 5 Some Indications for Referral to a Nephrologist

- Clinical findings inconsistent with typical diabetic nephropathy
- Massive proteinuria
- Hematuria, casts, and/or active urinary sediment
- AKI or rapidly declining eGFR
- Anemia of CKD
- Complex comorbidities (e.g., hyperparathyroidism or bone disease)
- Advanced CKD (eGFR <30 mL/min/1.73 m^2)

The discovery of AKI, as evidenced by a sustained increase of ≥50% in serum creatinine over a relatively short time, along with a rapid decrease in eGFR, warrants immediate evaluation and action (266,267). The risk of AKI is higher in people with diabetes than in the general population (266,267). Risk factors for AKI include nephrotoxic drugs, medications that alter renal hemodynamics, and intravascular volume reduction from medical conditions (e.g., hemorrhage, diarrhea, and emesis), diuretics, and antihypertensive medications. Decreased fluid intake and volume loss from nausea and vomiting in patients with adverse reactions to GLP-1 receptor agonists also pose a risk for AKI. The transient decrease in eGFR within days of initiating treatment with an SGLT2 inhibitor is not a manifestation of AKI, and evidence from RCTs confirms the renoprotective effects of these agents (5,6,53,156,161,251,256,257). All patients at risk for AKI should undergo appropriate assessment and prompt referral to a nephrologist for proper care (168,216,217,268).

See references starting on p. 34.

Dr. Dagogo-Jack is a professor of medicine and chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Tennessee Health Science Center in Memphis.