Screening for Kidney Disease in Adults With Diabetes

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Screening programs are generally aimed at conditions with a substantial public health impact and which benefit from early interventions. Chronic kidney disease (CKD), especially CKD attributed to diabetes, certainly fits this criterion. Diabetes remains the leading cause of end-stage renal disease (ESRD) in most countries in the world, accounting for 40–50% of incident ESRD cases (1–4). Due to the epidemic of diabetes secondary to obesity and the aging of the population, rates of kidney disease secondary to diabetes are on the rise. Within the past 2 decades, the incidence of ESRD secondary to diabetes in the U.S. has doubled while the prevalence of CKD among general Medicare patients diagnosed with both diabetes and hypertension has increased fourfold (1). Annual expenditures are highest for patients with ESRD secondary to diabetes compared with all other primary ESRD diagnoses (1). Thus, the epidemic of diabetes will certainly drive up health care costs for ESRD, which in the U.S. are projected to exceed $28 billion by 2010 (5). To prevent ESRD in individuals with diabetes, we must first do an adequate job of screening and detecting CKD. Unfortunately, the enormous burden of CKD remains undetected among adults with diabetes.

The early detection of CKD among patients with diabetes has primarily involved the measurement of urinary albumin excretion. A timed urine collection confirmed on at least two of three occasions over a 6-month period was the initial method of screening. The acceptance of the use of the albumin (in milligrams)-to-creatinine (in grams) ratio measured in a random urine specimen has greatly expanded screening efforts due to the test’s convenience for both patients and physicians. Persistently increased levels of urine albumin excretion ≥30–299 mg/24 h or spot urine albumin-to-creatinine ratios ≥30–299 mg/g indicate the presence of microalbuminuria while urine albumin excretion levels higher than this (=300 mg/24 h or albumin-to-creatinine ratio ≥300 mg/g in a spot urine sample) denote macroalbuminuria (also called clinical albuminuria or clinical proteinuria). Information on presence of urine albumin excretion in addition to level of glomerular filtration rate (GFR) may be used to stage CKD according to the National Kidney Foundation (NKF), and it is worthwhile to review how this staging system applies to people with diabetes (Table 1). This NKF classification is primarily based on GFR levels and therefore differs from some earlier staging systems used by others in which staging is based primarily on urinary albumin excretion, and only in stage 4 is there a decrease in GFR (6). In the NKF classification (7), stage 1 refers to patients who have evidence of some kidney damage (e.g., micro- or macroalbuminuria, hematuria, or other abnormalities in urine sediment or radiologic tests) that persists for >3 months in the setting of a normal or increased GFR. Patients with persistently increased urinary albumin excretion, including microalbuminuria, with normal or increased GFR would fit this stage. Stage 2 includes patients with evidence of kidney damage and a GFR between 60 and 89 ml/min/1.73 m². Stages 3–5 are based on GFR alone, and these patients may or may not have other evidence of kidney damage such as microalbuminuria. Stage 5 indicates kidney failure (GFR <15 ml/min/1.73 m²) and includes patients requiring renal replacement therapy (7). The clinical action plan for stage 1–3 includes the treatment of comorbid conditions and interventions for the slowing of CKD progression. Preparation for renal replacement therapy should be initiated during stage 4, while stage 5 indicates need for renal replacement therapy once uremia ensues (7).

Measuring urine albumin excretion as a screening tool for diabetic nephropathy is based on the well-characterized evolution of diabetic nephropathy in type 1 diabetes. The onset of type 1 diabetes is usually heralded by markedly elevated serum glucose levels and symptoms such as polyuria and polydypsia and therefore is detected and diagnosed early. After a period of ~10 years, ~10–28% of patients will develop microalbuminuria and 25–45% of patients with microalbuminuria will develop macroalbuminuria over the next 5–10 years (8). Only after the development of macroalbuminuria will GFR decline and potentially end in ESRD.

It has generally been accepted by the medical community that kidney disease among adults with type 2 diabetes follows the same clinical course and that increased urine albumin excretion is the earliest clinical evidence of kidney disease in this population. However, emerging epidemiologic data suggest that population patterns of CKD among adults with type 2 diabetes are not as uniform as those noted among adults with type 1 diabetes. Focusing solely on urine albumin excretion to screen for CKD may miss a substantial number of cases in adults with type 2 diabetes, a more heterogeneous group of patients who are generally older and have more comorbid conditions at diagnosis compared with adults with type 1 diabetes. Other etiologies for CKD,
which are not associated with increased urine albumin excretion, may be operable at the time of diagnosis of type 2 diabetes and over the course of their disease, such as renal vascular disease and cholesterol emboli. Up to one-third of adults with newly diagnosed type 2 diabetes already have CKD (9–13), and data suggest that in many of these patients CKD initially developed during the pre-diabetic state secondary to hypertension and other factors (14,15).

Cross-sectional studies have found decreased GFR in the absence of increased urine albumin excretion in a substantial percentage of adults with type 2 diabetes (16). In the Third National Health and Nutrition Examination Survey (16), which collected demographic and health information from a nationally representative sample of the U.S. population, 13% of adults with type 2 diabetes had a GFR <60 ml/min/1.73 m^2, consistent with stage 3 CKD. Among these adults with type 2 diabetes and decreased GFR, absence of increased urine albumin excretion (defined in this study as spot urine albumin-to-creatinine ratio ≥17 mg/g in men and ≥25 mg/g in women) was noted in ~40%, while absence of both increased urine albumin excretion and diabetic retinopathy was noted in 30%. The results did not change substantially when participants using ACE inhibitors were excluded (16).

Decreased GFR in the absence of increased urine albumin excretion among adults with both type 1 and type 2 diabetes has been reported in other studies. Tsalamandris et al. (17) noted substantial decreases in creatinine clearance among a subgroup of adults with diabetes who did not have increased urine albumin excretion. In their series of 40 adults with worsening kidney disease who were followed for 8–14 years (18 with type 1 and 22 with type 2 diabetes), 12 of these patients (4 with type 1 and 8 with type 2 diabetes) had normal urine albumin excretion (<20 μg/min) during the study period, yet creatinine clearance declined at a rate of 4 ml/min/year. Albumin excretion increased with or without a concomitant decrease in creatinine clearance in the remaining 28 patients. This same group of investigators (18) later measured GFR directly using the plasma disappearance of isotopic 99mTc-diethylene-triaminepenta-acetic acid among adults with type 2 diabetes followed at their outpatient clinic. In a group of 109 adults with type 2 diabetes with reduced GFR (<60 ml/min/1.73 m^2 BSA), 39% had normal urine albumin excretion (18). After excluding patients using medications that block the renin-angiotensin system, 23% with reduced GFR had normal urine albumin excretion. Over a 3- to 10-year follow-up period of 24 of these patients, rates of decline in GFR were −4.6 ± 1.0, −2.8 ± 1.0, and −3.0 ± 0.07 ml/min/year among patients with normal urinary albumin excretion, microalbuminuria, and macroalbuminuria, respectively (18). Thus, these studies demonstrate that substantial declines in GFR may be noted in adults with type 1 and type 2 diabetes in the absence of increased urine albumin excretion.

Because these studies did not perform kidney biopsies, investigators can only speculate on the etiology of decreased GFR in the absence of increased urine albumin excretion. Pathologic evidence of diabetic nephropathy has been documented in adults with diabetes even in the absence of increased urine albumin excretion (19,20). However, older patients with type 2 diabetes may also have vascular and tubulointerstitial changes due to the presence of comorbid conditions, including long-standing hypertension and renal vascular disease and potential senescence of glomeruli due to aging itself (21,22). Conversely, the presence of increased urine albumin excretion in adults with type 2 diabetes does not universally indicate the presence of classic diabetic glomerular pathology. Fioretto et al. (23) performed kidney biopsies in 34 adults with type 2 diabetes, serum creatinine <180 μmol/l (2.0 mg/dl), and microalbuminuria and no obvious signs of nondiabetic kidney diseases. Typical diabetic nephropathy was found in only 29% (n = 10). The other 24 had either normal or near-normal renal structure with minimal mesangial expansion or injury patterns atypical of diabetes with disproportionately severe renal structural lesions such as tubular atrophy and interstitial fibrosis, advanced glomerular arteriolar hyalinosis, or global sclerosis. Similar studies have also reported a range of biopsy findings from normal to typical diabetes changes and frequently other kidney diseases in adults with type 2 diabetes and increased urine albumin excretion (24,25).

The NKF and the American Diabetes Association (ADA) recommend screening all adults with type 2 diabetes for increased urine albumin excretion when they are first diagnosed with diabetes and at least annually thereafter (7,26,27). Adults with type 1 diabetes should be screened for increased urine albumin excretion annually after at least 5 years of diabetes duration (7,26,27). The NKF guidelines go one step further and also recommend the annual measurement of serum creatinine for the estimation of GFR in addition to measurement of urine albumin excretion (7). Currently, the ADA guidelines do not specify measuring serum creatinine when screening for nephropathy in adults with diabetes unless increased urine albumin excretion is identified and then confirmed in subsequent urine samples. However, it is now clear that stage 3 or higher CKD (GFR <60 ml/min/1.73 m^2) occurs in the absence of increased urine albumin excretion in a substantial proportion of adults with diabetes, and screening this population for increased urine albumin excretion alone will miss a considerable number of CKD cases. Thus, serum creatinine should be measured at least annually for the estimation of GFR in all adults with diabetes regardless of the degree of urine albumin excretion.

It should be emphasized that physicians should not rely on serum creatinine

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**Table 1—Stages of CKD**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73 m² BSA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderately decreased GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severely decreased GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 or dialysis</td>
</tr>
</tbody>
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*Kidney damage defined as abnormalities on pathologic, urine, blood, or imaging tests. Adapted from ref. 7.*
alone as a measure of kidney function but rather use the serum creatinine to estimate GFR and stage the level of CKD. Creatinine does not bind to proteins and is freely filtered by the kidney; thus, increases in serum creatinine over time usually represent changes in GFR. However, using the serum creatinine alone as a measure of kidney function is limited by the fact that serum creatinine levels depend on muscle mass, which differ by age and sex (28). The Cockcroft-Gault formula, which estimates creatinine clearance, incorporates age and body weight in order to account for age and sex differences in muscle mass (29).

\[
GFR = \frac{(140 - \text{age in years}) \times (\text{body weight in kilograms})}{(\text{serum creatinine (mg/dl)} \times 72)} \times (0.85 \text{ if female})
\]

Because this equation predicts creatinine clearance, which includes tubular excretion and intestinal catabolism of creatinine in addition to glomerular filtration (30), creatinine clearance may overestimate GFR by as much as 16–25% (31). In addition, this formula does not incorporate race, which may influence creatinine excretion (32). However, this prediction equation has been validated in several studies (33,34). A newer prediction formula, developed by Levey et al. (35) using demographic and laboratory data collected from subjects enrolled in the Modification of Diet in Renal Disease (MDRD) study, estimates GFR rather than creatinine clearance. The following equation estimated the GFR within 30% of the directly measured GFR in 91% of the MDRD participants.

\[
GFR = 186 \times (\text{plasma creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})
\]

This GFR prediction equation can be easily implemented and does not require a timed urine collection, but the validity of this equation remains questionable in patients with normal or increased GFR (36). Moreover, the MDRD study included very few Hispanics or Asians, and ~88% of the subjects were Caucasian. Although both the Cockcroft-Gault and MDRD formulas have limitations, either of these equations may be used to stage kidney disease in adults with diabetes and are far more accurate in adults in this regard than a simpler measurement of serum creatinine (31). These equations can most easily be used by going to a website in which the formulas are built in and the clinician simply has to supply age, race, and serum creatinine; a common website used is that of the NKF (www.kidney.org/kl/professionals/gfr_calculator.cfm). Serum creatinine concentration alone should never be used to assess the level of kidney function.

Screening tools work best when health care providers have a clear understanding of the natural history of the disease process (37). We may only now be truly appreciating the heterogeneous nature of CKD among adults with diabetes. Physicians caring for adults with diabetes must be aware that other comorbid conditions may influence the development of CKD in these patients and that these factors may have been operable before the onset of diabetes. Serum creatinine for the estimation of GFR should be measured at least annually in all adults with diabetes regardless of the degree of urine albumin excretion, in addition to measuring urine albumin excretion as recommended by the ADA (26,27). These additions to the current ADA recommendations will bring these guidelines into agreement with those of the NKF. By using screening tools that maximize sensitivity, we will be able to detect more CKD cases and detect them earlier when interventions are most successful. In addition, by finding decreases in GFR in certain patients without increased urine albumin excretion and especially in the absence of retinopathy, consideration has to be given to other possible causes of progressing CKD that might need specific interventions.

References


15. Tapp RJ, Shaw JE, Zimmet PZ, Balkau B, Chadban SJ, Tonkin AM, Wellborn TA, Atkins RC: Albuminuria is evident in the


