

Optimal Early Diagnosis and Monitoring of Diabetic Kidney Disease in Type 2 Diabetes Mellitus: Addressing the Barriers to Albuminuria Testing

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Abstract

Chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) is associated with increased risk of end-stage renal disease (ESRD) and cardiovascular disease (CVD). Urine albumin-to-creatinine ratio (UACR) is a sensitive and early indicator of kidney damage, which should be used routinely to accurately assess CKD stage and monitor kidney health. However, this test currently is performed in only a minority of patients with T2D. Here, we review the importance of albuminuria testing and current barriers that hinder patient access to UACR testing and describe solutions to such testing in a community clinical setting.

Keywords

Diabetic nephropathies, Renal insufficiency, chronic, Diabetes mellitus, Chronic kidney disease, Diabetes, Urine albumin-to-creatinine ratio, UACR, Albuminuria, Screening, Monitoring

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Introduction

Chronic kidney disease (CKD) is characterized by elevated urinary albumin excretion (albuminuria) or reduced estimated glomerular filtration rate (eGFR).^{1,2} Ultimately, CKD can progress to end-stage renal disease (ESRD), requiring dialysis or kidney transplantation.³

CKD attributed to diabetes is a common complication, occurring in 36% to 40% of patients.^{3,4} CKD may be present at diagnosis of type 2 diabetes (T2D); in patients with type 1 diabetes, CKD typically develops 10 years after onset of the disease.³ Patients with diabetes have an increased risk of cardiovascular disease (CVD), which is further elevated in patients with concomitant CKD,⁵ and CVD is the primary cause of death in patients with CKD.⁶

Multiple guidelines recommend assessment of kidney function in patients with diabetes using estimated glomerular filtration rate (eGFR), calculated using the CKD Epidemiology Collaboration (CKD-EPI) formula, whereas architectural kidney damage (albuminuria) should be measured using urine albumin-to-creatinine ratio (UACR).^{2,3,7} CKD is defined as albuminuria above the normal range (UACR ≥ 30 mg/g), and/or reduced kidney function (eGFR < 60 mL/min/1.73 m²) present for > 3 months in the absence of signs or symptoms of

other primary causes of kidney damage.^{2,3,7} However, elevated albuminuria (ie, UACR ≥ 30 mg/g) in the presence of normal to mildly decreased eGFR (eGFR 60 to ≥ 90 mL/min/1.73 m²), and normal albuminuria (ie, UACR < 30 mg/g) coupled with moderately to severely decreased eGFR (eGFR < 60 mL/min/1.73 m²) are also indicators of increased CKD risk.² High albuminuria (microalbuminuria; 30–300 mg/g) can be undetectable, or can be misclassified into lower risk categories, through conventional urine colorimetric test strips (dipsticks).⁸ Very high albuminuria describes albuminuria levels of ≥ 300 mg/g, often described as macroalbuminuria.⁹ However, micro- and macroalbuminuria are terms no longer used by the guidelines.^{2,3}

Early screening for CKD using UACR is key, particularly in the initial stages, as early kidney disease is often asymptomatic and is typically associated with normal or

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high eGFR, and thus requires detection using laboratory tests.¹⁰ UACR can potentially identify CKD long before cardiovascular (CV) and kidney manifestations become evident.^{11,12} Indeed, up to half of all patients at high risk of kidney failure may be unaware of their kidney status.¹³ The clinical importance of CKD is such that the recently updated American Diabetes Association (ADA) 2021 practice guidelines recommend, at minimum, annual UACR and eGFR assessment in all T2D patients regardless of treatment. In patients with diabetes and existing CKD with higher risk of progression, UACR and eGFR should be monitored more frequently to guide ongoing treatment decisions.³ The US Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) groups also recommend UACR and eGFR assessments for patients with diabetes.^{2,7,14} Moreover, annual assessment of kidney function is likely to form part of a new Healthcare Effectiveness Data and Information Set (HEDIS) quality measure, thereby affecting future physician reimbursements under Medicare and other US medical insurance schemes.¹⁵

Despite the widespread practice of eGFR screening, rates of UACR testing in patients with T2D in the United States remain suboptimal.^{4,16,17} The Awareness, Detection and Drug Therapy in Type 2 Diabetes and Chronic Kidney Disease (ADD-CKD) study reported that at baseline, more patients had eGFR assessment than UACR testing (85% vs 47%, respectively).¹⁶ This was even lower in the Center for Kidney Disease Research, Education and Hope (CURE-CKD) registry of patients with T2D at risk of CKD, where only 8.7% (52 551/606 064) had been tested for albuminuria at baseline.¹⁷

This commentary reviews the importance of albuminuria testing and current barriers that hinder patient access to UACR testing. The article aims to improve awareness of the importance of regular monitoring of kidney function in patients with T2D and to describe solutions to testing in a community clinical setting.

The Importance of Monitoring Albuminuria in Patients with T2D

Traditionally, CKD was described as a linear progression from kidney hyperfunction and hypertrophy, to increasing albuminuria, decreasing eGFR, and ultimately ESRD.^{18,19} This model has been abandoned since the emergence of US epidemiological data from the National Health and Nutrition Examination Survey (NHANES). Between 1988 and 2014, the prevalence of high albuminuria declined by 24% ($P < .001$), very high albuminuria rates remained stable ($P = .22$), and rates of declining eGFR rose sharply ($< 60 \text{ mL/min/1.73 m}^2$, 61% [$P < .001$]; $< 30 \text{ mL/min/1.73 m}^2$, 186% [$P < .004$]).²⁰ These opposing trends reflect recent discoveries that albuminuria may undergo

remission/regression and that eGFR loss, once initiated, progresses inevitably to ESRD.¹⁹ Therefore, albuminuria does not necessarily precede eGFR loss, and kidney function may decline independently of albuminuric status.^{19,21} As a result, three phenotypes of CKD are now recognized: eGFR decline only, albuminuria only, and both eGFR decline and albuminuria.¹⁹

However, albuminuria remains a key diagnostic indicator. Recently, changes in albuminuria have been shown to be associated with early structural changes observed on kidney biopsy,²¹ changes in albuminuria are prognostic of disease progression or regression,⁹ and raised absolute levels of albuminuria predict poor outcomes.^{22,23} In a meta-analysis including 128 505 patients with diabetes, all-cause mortality and CV mortality risks were significantly increased in those with high albuminuria (73% and 81%, respectively) compared with those with undetectable albuminuria.²² In a second meta-analysis by the same group, including 637 315 individuals without history of CV disease, it was found that UACR was a sensitive predictor of coronary heart disease, stroke, or heart failure over 5 years, especially in subjects with diabetes.²³ In general, high albuminuria is a sign of early kidney damage, and even urinary albumin excretion rates within the normal range are important prognosticators of kidney and CV outcomes, and excess all-cause mortality.^{22,24-26}

Analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD; $n = 10\,185$ patients with T2D) study showed that albuminuria alone appears to be a greater predictor of risk for some kidney and CV outcomes compared with eGFR decline alone.²⁷ There was no increased risk of ESRD over 10 years for patients with eGFR decline only compared with those with normal kidney function. Also, while eGFR decline increased risks (hazard ratio [HR]: ~ 1.4) of all-cause mortality and major CV events compared with normal kidney function, risk of these same outcomes was significantly greater in patients with albuminuria only (HR: $\sim 1.8-1.9$) or albuminuria plus eGFR decline (HR: ~ 2.4).²⁷

Albumin, when present in the glomerular ultrafiltrate, behaves as a pro-inflammatory and pro-fibrotic protein that actively contributes to CKD pathogenesis.⁹ Reducing tubular exposure to albumin, therefore, may be beneficial.⁹ In patients with T2D and high albuminuria, patients who achieved a $\geq 50\%$ reduction in albuminuria over 2 years had a significantly smaller decline in kidney function (-1.8 mL/min/year) compared with those who did not ($-3.1 \text{ mL/min per year}$).²⁸ In a study of losartan in patients with T2D and nephropathy ($n = 1513$), a $\geq 50\%$ reduction in albuminuria over the first 6 months resulted in a 27% reduction in the risk of heart failure.²⁹ This is further supported by a meta-analysis, which revealed that smaller (30%) reductions in albuminuria over 6 months conferred a 27% lower HR for the composite endpoint of ESRD, eGFR $< 15 \text{ mL/min/1.73 m}^2$,

or doubling of serum creatinine, suggesting that even modest reductions in albuminuria confer a clinical benefit to patients.³⁰

Regular monitoring of urinary albumin excretion in patients with T2D is therefore an essential tool in the detection of the onset of CKD, monitoring of disease progression, collection of kidney and CV prognostic data, and guidance in treatment decision-making. The UACR is recommended by national guidelines to assess albuminuria as ratio of urinary albumin to creatinine, the latter of which in light of its constant excretion pattern, corrects for urine volume.^{2,7} When compared with other available measures of albuminuria (eg, 24-hour urinary total protein excretion, 24-hour urinary albumin excretion, and urinary albumin concentration), the UACR demonstrated the highest accuracy for predicting kidney events in patients with kidney disease and T2D.³¹ Moreover, 24-hour urine samples are often difficult to collect. Furthermore, urine colorimetric test strips are inadequate for assessing albuminuria as they are insufficiently sensitive, not standardized across manufacturers, not quantitative, and have been associated with underestimation of CKD risk compared with UACR.^{2,8}

Current Barriers to UACR Screening

Practical Barriers Hindering Patient Access

Facilities at community practitioners' offices may not always be designed for straightforward collection of urine samples. In our experience, outpatient facilities may lack or not fully follow a well-established protocol for urine collection, and the patient may not be adequately instructed on how to provide a sample. Patients may therefore face an inconvenient and inefficient procedure for urine collection that can decrease compliance. In particular, most patients do not submit the first morning void for testing as is recommended, particularly for those patients scheduled for office visits in the afternoon. Ready patient kits that can be used at home, including guidance and sample collection vessels, may increase compliance. Patient education is also an important part of adoption of UACR screening. The US National Institute of Diabetes and Digestive and Kidney Diseases has developed patient education materials (available at: <https://www.niddk.nih.gov/health-information/professionals/advanced-search/explain-kidney-test-results>) that provide background information on kidney function and disease, the rationale and implications of testing, and lifestyle modifications that may assist with preserving kidney function.

In addition, technicians at outpatient facilities routinely carry out blood work, but are less likely to obtain urine samples; therefore, the opportunity to obtain and conduct UACR testing may often be missed. Electronic/physical reminders, wall charts, and other simple aids may improve testing rates.

Access to UACR testing may be improved by using Clinical Laboratory Improvements Amendments (CLIA)-waived point of care UACR testing options, that is, those approved for use closer to the patient and not necessarily in a central laboratory. These may be billed to medical insurance providers.

Challenges Limiting UACR Testing

Ordering rates for UACR testing by clinicians may be low due to the current exclusion of UACR from laboratory panels used for monitoring general health. Whereas serum creatinine and eGFR assessments are included in basic and comprehensive metabolic panels, the UACR is more specific to kidney disease testing.³² As a result, UACR monitoring may be overlooked due to lack of awareness.

Even when UACR testing is required, other issues may affect the results obtained. A study looking at urine protein testing in two primary care organizations found that UACR reporting rates were low because some providers were unaware of the difference between UACR and total urine microalbumin, and laboratories were also erroneously reporting urine microalbumin results when a UACR test had been ordered.³³ Furthermore, there is a lack of harmonization in urine albumin result reporting from different testing facilities (it may be reported as a concentration or timed excretion, or indexed to creatinine), which can lead to difficulties in test result interpretation.¹

These issues may be at least partially resolved through the adoption of the National Kidney Foundation (NKF)/American Society for Clinical Pathology (ASCP) Kidney Profile, consisting of standardized eGFR (based on the CKD-EPI creatinine 2009 eGFR equation) and UACR assessment. The Kidney Profile is distinct from the Renal Function Panel (CPT 80069), which is used only for monitoring individuals with diagnosed CKD. The goal of the Kidney Profile is to detect and monitor CKD. The NKF and ASCP are currently recommending industry-wide implementation of this kidney panel, which may be ordered through a single click or stroke.³⁴ To provide higher quality of chronic disease management, the latest ADA guidelines recommend alignment with the core elements of the Chronic Care Model, including health system, community, clinical information systems (eg, timely access to patient data), decision support for providers (eg, access to evidence-based guidelines), delivery system design (eg, proactive care delivered by multidisciplinary teams), and patient self-management support.^{3,35} In this context, there are many opportunities to apply information technology to improve and scale chronic disease management.³⁶⁻³⁸ Electronic health records could significantly improve care management for CKD in patients with T2D, including optimizing CKD early screening and detection.^{38,39}



	 ACTION	 OPTIMIZATION
Test Ordering	<ul style="list-style-type: none"> At diagnosis of T2D - screen patients with UACR (kidney damage) and eGFR (kidney function)³ At diagnosis of T2D + CKD - monitor at least annually using UACR and eGFR assessments, and more frequently if kidney damage or kidney function is severely reduced³ 	<ul style="list-style-type: none"> Adopt automatic test reminder system and/or electronic/physical reminders, wall charts, and other aids Adopt the NKF/ASCP Kidney Profile test panel and other available electronic clinical decision support systems Use CLIA-waived point of care UACR testing options, if available
Patient Testing	<ul style="list-style-type: none"> Assess urine albumin in random spot urine samples from first morning voids^{2,3,6,40} If inconvenient, take a random urine specimen; if albuminuria is suspected, the test should be repeated with a first morning void⁴⁰ Store samples according to recommendations (4–8°C for up to 1 week; ≤-70°C for longer)⁴⁰ 	<ul style="list-style-type: none"> Schedule morning patient appointments Adopt ready patient kits, including guidance and sample collection vessels
Interpretation of Test Results	<ul style="list-style-type: none"> If albuminuria is detected, repeat the UACR test at least twice for confirmation^{2,3} Refer patients with a UACR measurement >300 mg/g for specialist (nephrologist) assessment 	<ul style="list-style-type: none"> Physicians should be familiar with the standards for the test for the specific laboratory used
Treatment	<ul style="list-style-type: none"> In patients with T2D and confirmed albuminuria and no signs/symptoms of other primary causes of kidney damage, introduce and titrate ACEi/ARB to maximum tolerated dose^{2,3,6,12} Continue UACR monitoring to evaluate disease progression and response to treatment³ 	

Figure 1. Albuminuria testing points for patients with T2D.

Better use of information technology and clinical decision support systems,⁴⁰ for example, automatic ordering of UACR tests and/or checklists detailing when and how to test, can improve rates of UACR testing and reporting. An electronic clinical decision support system providing automatic individualized guidance on patient management and education has been successfully integrated in a recent trial.⁴¹

Standardization and Quality of UACR Screening

Preanalytical Considerations

Urine albumin measurements can vary from day-to-day within individuals^{10,42,43} and can be confounded by numerous factors such as menstrual bleeding, urinary tract infections, posture (orthostasis), and strenuous exercise.^{1,2,44,45} Therefore, guidelines recommend that patients with a positive result for albuminuria undergo confirmatory testing (Figure 1).^{2,3} Two of three UACR test results should be abnormal (30–300 mg/g) before a diagnosis of albuminuria is made.^{2,3}

How urine samples are collected can also affect the results obtained. Guidelines recommend that UACR be assessed in a random spot urine sample in the first morning

void (to avoid effects of exercise and to standardize posture by ensuring prolonged recumbency before collection).^{2,3,7} If this is not convenient, a random urine specimen may be taken; if the UACR result is above normal limits, the test should be repeated with a first morning void.⁴⁶ Timed 24-hour urine collections are usually not required for calculation of the UACR,⁴⁶ as they do not increase accuracy over untimed collection.³

Best practice is for fresh urine samples to be refrigerated at 4° to 8°C for 1 week only or frozen at –70°C or lower if longer storage is required.⁴⁶

Lack of Standardization in Urine Albumin Measurement

At present, urine albumin measurement is not standardized,⁴⁵ which may affect the quality/accuracy of test results; UACR values that are close to cutoff limits may be classified incorrectly.⁴⁶ Each testing laboratory will have their own definitions for cutoffs for their specific test; therefore, it is also vital that the patient's physician be aware of the standards for the test for the specific laboratory used.

A standardization program for urine albumin testing was initiated in 2008 by the National Kidney Disease Education Program, the International Federation of Clinical Chemistry,

and other parties, but this is not yet complete.⁴⁶⁻⁴⁸ Three key areas to improve UACR agreement between laboratories have been identified: reference materials to enable standardized calibration of urine albumin testing, regardless of the methodology employed; a reference measurement procedure, including standardized reporting of results, cutoff values, and reference intervals; and reference laboratories to assist manufacturers with validation during the development of urine albumin tests.^{44,45,47} Once urine albumin measurement has been standardized, an educational program should be implemented to provide information on best practice.⁴⁷

Example Model of Best Practice for UACR Assessment and Next Steps

A patient with T2D should be screened for CKD at the time of diagnosis and monitored regularly (at least annually) using UACR and eGFR assessments.³

Urine albumin levels should be assessed in a random spot urine sample in the first morning void, and the results reported as the UACR, given in mg/g or mg/mmol.⁴⁶ If a positive result for albuminuria (30-300 mg/g) is obtained, the UACR test should be repeated at least twice in the 3- to 6-month follow-up period for confirmation.^{2,3} Patients with a UACR measurement >300 mg/g should be referred for specialist assessment.²

Once albuminuria has been confirmed in a patient with T2D, and no signs/symptoms of other primary causes of kidney damage are detected, recommendations made in the KDIGO, KDOQI, and ADA guidelines should be followed regarding appropriate interventions for CKD in patients with T2D. Blood pressure and CV risk should be addressed in addition to glycemic control. This may be achieved using pharmacologic interventions as clinically indicated (eg, use of an angiotensin-converting enzyme inhibitor [ACEi]/angiotensin receptor blocker [ARB], statins, and sodium-glucose transporter-2 inhibitor [SGLT-2i]).^{2,3} The KDOQI, KDIGO, and ADA guidelines all recommend use of ACEi/ARB in patients with CKD and incorporate UACR measurements to guide therapeutic decision-making.^{2,3,7,14} In the absence of intolerance or contraindications, ACEi/ARB agents should be titrated to the maximum approved dose for the treatment of hypertension.¹⁴ Patients with albuminuria receiving ACEi/ARB therapy should undergo continued UACR monitoring to evaluate disease progression and response to treatment.³

Conclusions

At present, CKD in patients with T2D is underdiagnosed. Early screening for CKD is recommended, and if CKD is confirmed, follow-up testing should be repeated at least twice annually. Optimal screening for CKD is achieved by

measuring the UACR in a spot urine sample (first morning void) and by estimating the GFR from serum creatinine measurements. Current issues surrounding the lack of standardization in UACR testing can be resolved with the implementation of the urine albumin measurement standardization program. Routine eGFR and UACR screening may increase awareness of the prevalence of CKD in the T2D population and ultimately result in improved patient outcomes.

Once CKD has been diagnosed, appropriate intervention with guidelines-recommended therapy can be initiated and should be optimized for individualized-patient targets for glycemic and blood pressure control, with specialist referral as necessary.

Declaration of Conflicting Interests

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