

Laboratory Assessment of Diabetic Kidney Disease

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■ **IN BRIEF** Regardless of etiology, chronic kidney disease (CKD) is identified by two laboratory tests: 1) estimated glomerular filtration rate (eGFR), a measure of kidney function, and 2) urine albumin-to-creatinine ratio (UACR), a measure of kidney damage. It is crucial for all health professionals to understand the significance and limitations of these tests to appropriately identify CKD patients, guide therapy, and determine prognosis. This article provides information that will enable diabetes educators and other clinicians to properly interpret eGFR and UACR laboratory results in the identification and management of CKD.

Chronic kidney disease (CKD), regardless of etiology, is identified as a *decrease in kidney function* and/or evidence of *kidney damage* (1). Generally, a decrease in kidney function is described by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m². Kidney damage, especially in glomerular disease such as diabetic kidney disease (DKD), is generally reflected by increased urinary excretion of albumin. Because these two measures are used for identifying patients, guiding therapy, and establishing prognosis, it is crucial for all health professionals to understand the important information these laboratory tests convey, as well as their limitations.

eGFR

The kidney functions, in a broad sense, as a filter. Kidney function has traditionally been assessed using serum creatinine, a metabolite of muscle that is freely filtered and excreted by the kidney. However, baseline serum creatinine reflects an individual's muscle mass. Thus, the same creatinine value may reflect a different level of kidney function in

a young, muscular person than in a frail, elderly individual.

To overcome this variability in creatinine generation, equations to estimate GFR have been developed that utilize serum creatinine but also include other variables that affect muscle mass and hence creatinine (2). These variables, used in the two most common estimating equations, include age, sex, and race. Younger age, male sex, and African heritage are associated with greater muscle mass and therefore higher creatinine excretion. For example, a creatinine of 1.2 mg/dL in a 78-year-old white woman is associated with an eGFR of 43 mL/min/1.73 m², whereas the same creatinine level in a 28-year-old African-American man is associated with an eGFR >60 , reported as normal.

Another confounding factor is the loss of kidney function associated with age. Because the definition of CKD (eGFR <60 mL/min/1.73 m²) is not age-adjusted, some patients with age-related loss of kidney function may be labeled as having CKD when it is not clear there is a disease process (3).

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eGFR is clearly a better tool for patient management than serum creatinine alone, but it is important to remember it is an *estimate* and not the *measured* GFR. Repeated determinations and establishment of trends over time may be key to understanding kidney function in an individual with diabetes. Figure 1 provides a visual guide developed by the National Kidney Disease Education Program (NKDEP) for interpreting eGFR results.

Albuminuria

An abnormal amount of albumin in the urine is the most commonly measured marker of kidney damage. Normally, very little albumin is excreted in the urine. Most of the albumin that passes through the glomerulus is reabsorbed in the tubules of the nephron. Damaged kidneys allow more albumin to cross the glomerular filter into the urine, exceeding the tubules' ability to reabsorb. Glomerular disease, including diabetic nephropathy, is characteristically associated with increased excretion of albumin. Increased urine albumin is also a marker for cardiovascular disease and hypertension and, in these circumstances, is thought to be a marker of generalized endothelial dysfunction. Figure 2 shows the association between albuminuria and risk of renal events (4,5).

Thirty mg albumin/day has been conventionally accepted as the upper limit of normal for urine albumin excretion. The conventional urine dipsticks become 1+ positive at a concentration of 30 mg/dL albumin, equivalent to 300 mg/L or—if assuming a daily urine output of 1 L of urine—300 mg/day. The range of urine excretion above the normal of 30 mg/day and below the dipstick sensitivity of 300 mg/day has traditionally been called *microalbuminuria*. Urine excretion >300 mg/day has been called *macroalbuminuria* or *clinical albuminuria*. However, albuminuria appears to be a continuous biomarker, and the

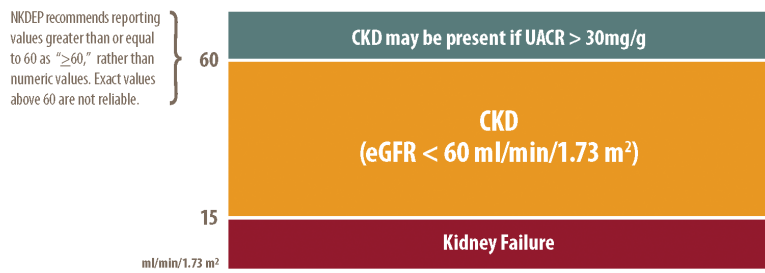
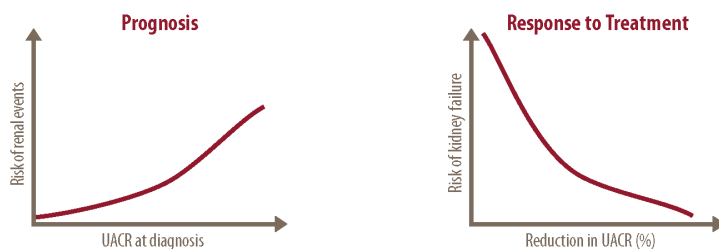


FIGURE 1. Interpreting eGFR results. An eGFR ≥ 60 mL/min/1.73 m² is considered normal unless albuminuria is present. Exact values >60 mL/min/1.73 m² are not reliable and should be reported simply as “ >60 .” An eGFR <60 mL/min/1.73 m² may indicate CKD, and an eGFR <15 mL/min/1.73 m² may indicate kidney failure.



In a large cohort of CKD patients, a higher UACR at time of diagnosis was associated with increased risk for renal events—loss of half of eGFR, dialysis, or death. (Chronic Renal Insufficiency Cohort study)

A randomized trial of diabetes patients with CKD found that the greater the reduction of UACR in response to treatment (with ARBs), the lower the risk of progression to kidney failure. (De Zeeuw D, et al. *Kidney International*, 2004;65:2309-2320)

FIGURE 2. UACR and risk of renal events. In a large cohort of CKD patients, a higher urine albumin-to-creatinine ratio (UACR) at time of diagnosis was associated with increased risk for renal events (i.e., loss of half of eGFR, dialysis, or death). A randomized trial of diabetes patients with CKD found that the greater the reduction of UACR in response to treatment with angiotensin receptor blockers, the lower the risk of progression to kidney failure. Graphs adapted from the Chronic Renal Insufficiency Cohort (left) (4) and Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (right) (5) studies.

distinction between values higher or lower than 300 mg/day does not reflect a physiological barrier, but merely the sensitivity of the clinical measuring tools that have been available. With the wide use of techniques to measure low levels of albuminuria, the terms microalbuminuria and macroalbuminuria will likely disappear.

We use the urine albumin-to-creatinine ratio (UACR) to assess urine albumin excretion (6). This test uses a ratio between the concentrations of albumin and creatinine in a spot urine specimen to estimate albumin excretion over 24 hours. The ratio in

the spot specimen correlates well with 24-hour excretion because urine creatinine excretion is approximately 1 g/day. The result is usually reported as mg albumin/g creatinine and is equivalent to mg albumin excreted/day. Because urine albumin excretion in an individual may vary from day to day or even hour to hour, it is crucial that measurements of urine albumin are repeated on two or more occasions before diagnosing abnormal albuminuria, and, wherever possible, early-morning, first-void specimens are collected. Bear in mind that UACR will tend to underestimate urine albumin excretion in

people who have greater muscle mass and excrete larger quantities of creatinine in the urine, and overestimate urine albumin excretion in people who have less muscle mass and excrete lower quantities of creatinine in the urine. Thus, using the same 30 mg/g cutoff for men and women may overestimate the prevalence of abnormal albuminuria in women relative to men (7). Similarly, differences in race and age may also affect UACR results.

eGFR, UACR, and the Natural History of DKD

Figure 3 demonstrates the changes in eGFR and UACR with diabetes duration that occur in people with diabetes who are developing nephropathy. Early in the course of diabetes, there is an increase in GFR, termed *hyperfiltration*, associated with hyperglycemia (8). After a few years, the GFR starts to decline, although from an elevated level. At about the time the GFR reaches the pre-hyperglycemic level, which appears normal, urine albumin begins to increase (9). Thus, elevations of urine albumin are often the first clinical sign of DKD. Over subsequent years, as kidney disease progresses and GFR decreases, albuminuria increases. Albuminuria may start decreasing as GFR becomes severely reduced.

Limitations to eGFR and UACR

Laboratory reporting of eGFR routinely with serum creatinine is nearly universal, and utilization of UACR to assess urine albumin is recommended by many clinical guidelines. Although widespread adoption of these laboratory tools has likely improved the identification of people with diabetes and kidney disease, it is crucial for clinicians to understand the limitations of these tests to implement them most appropriately in patient management.

Limitations to eGFR

The most commonly used estimating equations have been developed in study populations where participants

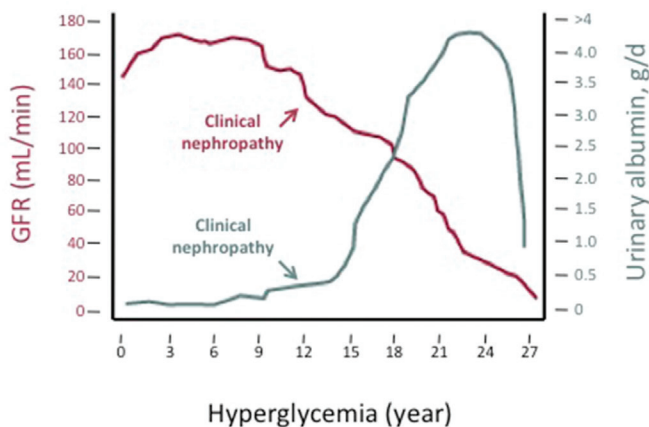


FIGURE 3. Natural history of diabetic nephropathy. Hyperfiltration associated with hyperglycemia may occur in early diabetes. With increasing damage to the kidneys, GFR starts to decline from the elevated hyperfiltration level. As GFR returns to the pre-hyperglycemic level, urine albumin begins to increase. Adapted from ref. 22.

have had formal measurements of GFR (mGFR). The equations were developed through a process called regression and perform well in describing kidney function in *populations* of patients. However, performance in *individual* patients is less precise, and clinicians must keep this in mind if they are to best serve each patient. The performance characteristic used to describe these equations is the P30, the percentage of eGFR results within 30% ± of the mGFR. The P30 of the commonly used equations is in the 80–90% range. This means that, for a patient with an eGFR reported as 60, there is an 80% likelihood that the actual mGFR is between 48 and 72. The higher the eGFR, the broader the range (i.e., as a number gets bigger, ± 30% also becomes bigger, and the eGFR is less precise). For this reason, many labs do not report eGFR results >60 mL/min/1.73 m² as a number but rather as “>60” (10). Because laboratories often report results <60 as CKD and assign a stage (usually not explained), it is crucial that the imprecision of eGFR be understood.

There are many circumstances in which any creatinine-based estimate of kidney function, including eGFR, should not be used. Creatinine-based estimates should be avoided

in patients with changing serum creatinine levels (as occurs in many hospitalized patients); people with acute kidney injury; people with extremes in muscle mass, body size, or altered diets; and people taking medications that affect excretion of creatinine (e.g., trimethoprim).

Limitations to Albumin

Although measurement of urine albumin is widely used for predicting prognosis and monitoring response to therapy, there are limitations to this test, as well. Not all people with DKD and decreased eGFR demonstrate elevated albumin excretion. In the U.K. Prospective Diabetes Study, only 35% had an increased urinary albumin concentration before developing reduced renal function (11). Regardless, people with diabetes and decreased eGFR but without increased albuminuria should undergo a screening evaluation to identify the presence of nondiabetic kidney disease (12).

The measurement of urine albumin is not standardized and demonstrates significant imprecision. Recently, the most common assays were compared to a “gold standard” isotope dilution mass spectrometry assay and were found to vary by ~40% across a broad range of albumin concentrations from very low

(13 mg/L) to high (1,084 mg/L) (13). In addition, urine albumin results are reported in a variety of formats, which increases confusion and decreases providers' understanding of their interpretation. The NKDEP Laboratory Working Group and the National Institute of Standards and Technology, which standardized the laboratory measurement of serum creatinine, are now collaborating with the International Federation of Clinical Chemistry to standardize the laboratory measurement and reporting of urine albumin (14).

Using eGFR with UACR to Identify and Monitor DKD

Even with standardization of serum creatinine and urine albumin measurement, there is significant variability within each individual and between individuals in predicting progression (15). Clinicians should be cautious when predicting prognosis based on any single measurement for either biomarker. Serial monitoring is likely to reduce confounding "noise" and establish a temporal trend that may be more informative for prognosis.

Although albuminuria is widely used to assess kidney damage, the link between hyperfiltration, albuminuria, and progressive loss of GFR has not been consistently demonstrated in animal or clinical studies (16). The acute decrease in GFR seen with use of renin angiotensin system (RAS) antagonists, although associated with decreased albumin excretion and slower loss of GFR, may confuse clinicians.

Screening

Most clinicians are aware of the significant burden of CKD and the growing cost of end-stage renal disease treatment. However, there is uncertainty about whom and when to screen and how to monitor patients once a diagnosis is made. Conflicting advice from the U.S. Preventive Services Task Force (USPSTF), the kidney disease community, and the American College of Physicians (ACP) has

left clinicians confused about screening and monitoring patients.

The Agency for Healthcare Research and Quality (AHRQ) published an evidence review in 2012 (17) that found no randomized controlled trials evaluating screening and monitoring in early CKD. However, the review did identify indirect evidence that screening could identify patients with undiagnosed CKD and that effective treatments did exist. Based on this review, the USPSTF did not recommend screening asymptomatic adults, but specifically excluded chronic disease management, particularly diabetes and hypertension, from its conclusions (18). The ACP Clinical Guideline Committee published recommendations in 2013 on screening, monitoring, and treatment of stages 1 to 3 CKD (19). Based on the AHRQ evidence review, the committee made two recommendations regarding screening and monitoring: 1) against screening for asymptomatic adults without risk factors and 2) against albuminuria testing for patients, including those with diabetes, who are already treated with an ACE inhibitor or angiotensin II receptor blocker. It may have been more reflective of scientific knowledge for the guideline committee to state simply that there was no evidence to support patient benefit from albuminuria monitoring in people with CKD rather than making a recommendation against such monitoring (grade: weak recommendation, low-quality evidence).

Clinical studies in CKD have historically employed a limited range of endpoints (e.g., loss of half of GFR, dialysis, or death), and change in albuminuria has not been a primary endpoint. However, there are extensive data showing a strong association, especially in diabetes, between increased albuminuria and poor prognosis (20) and a similar association between improvement in albuminuria after initiation of RAS antagonist treatment with decreased risk of renal endpoints (5).

The potential of albuminuria to monitor and guide therapy has yet to be proven. However, this inexpensive test is a clinically useful tool to identify patients at risk for rapid progression, to help educate about CKD, and to promote self-management. Analysis of laboratory data from large cohorts of CKD patients confirms the importance of quantifying albuminuria for prognosis. Patients with diabetes and increasing albuminuria are at high risk of progressive loss of GFR and eventual kidney failure. These findings are reflected in the inclusion of level of urinary albumin excretion in widely used staging algorithms (1).

National Health and Nutrition Examination Survey data indicate that >10% of the U.S. population may meet laboratory diagnostic criteria for CKD (21). The benefits of population management for adults with age-related decreases in kidney function or transient low-grade albuminuria are unproven. Indeed, primary care providers are, perhaps, a bit weary of automated alerts about elderly patients with mildly decreased eGFR who have suddenly been identified with "stage 3 CKD." For busy practitioners, the crucial issue is to identify which of their patients are at risk of progression and for whom more aggressive management may provide important benefits. Quantitative albuminuria testing to identify and monitor patients with CKD, including those being treated with RAS antagonists, is an inexpensive tool that may help clinicians identify patients who would benefit most from more intense management. Clinicians may wish to continue using albuminuria to guide management while we await high-quality evidence from controlled trials that test change in urinary albumin excretion as a primary endpoint.

Unanswered Questions

Recent differences in guideline recommendations emphasize the need for more and better evidence. If we

are to continue to make progress in identifying and managing DKD, it is important that we seek answers to a number of questions, including:

1. What are the reporting cutoffs for the definition of normal albuminuria?
2. Should there be sex-specific albuminuria cutoffs that identify patients at increased risk of cardiovascular disease as well as of kidney disease?
3. Is there a practical protocol for screening patients that reduces intra-individual variability (e.g., random UACR confirmed with first-void UACR)?
4. What are the algorithms to predict risk for progression of DKD, and which factors must be incorporated (e.g., eGFR, UACR, rate of change in eGFR or UACR, blood pressure, new biomarkers)?
5. What is the role of urine albumin monitoring in guiding therapy? Is there a strategy to target aggressive management to patients at greatest risk of progression to kidney failure (e.g., patients on single-agent RAS blockade therapy with a rapidly declining eGFR of >5 mL/min/1.73 m²/year)?

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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