

Glomerular Filtration Rate and Albuminuria: Twin Manifestations of Nephropathy in Diabetes

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In the past three decades, urinary albumin excretion has assumed a central role in the diagnosis and management of kidney disease among people with diabetes, both type 1 and type 2. Microalbuminuria was initially found to predict subsequent overt albuminuria (dipstick positive, or ≥ 300 mg/24 h), which in turn predicted loss of GFR (1–3). From the strength of these relationships, it has frequently been assumed that microalbuminuria and overt albuminuria are requisite first and second steps along a single pathway that leads to loss of GFR and ESRD.

In recent work, Perkins *et al.* (4) challenged these assumptions by demonstrating that microalbuminuria can regress to normoalbuminuria among people with type 1 diabetes. In this issue of the *Journal of the American Society of Nephrology (JASN)*, these authors build on their previous work by examining change in GFR (estimated as 100/serum concentration of cystatin C) among patients from the same cohort (5); 578 patients with urine albumin excretion rates that were consistently < 300 $\mu\text{g}/\text{min}$ were followed for 8 to 12 yr. Loss of GFR was defined as an average change in estimated GFR (eGFR; “slope”) that exceeded $-3.3\%/yr$, a threshold that represents the 2.5th percentile of age-standardized eGFR decline among participants without diabetes in the Baltimore Aging Study. Persistent microalbuminuria was a strong risk factor for subsequent loss of GFR, reemphasizing earlier work that established the importance of sustained increases in urine albumin excretion in the pathogenesis and diagnosis of diabetic kidney disease. However, patients who lost GFR at a high rate did not have overt albuminuria, by study design, and some had “normal” urinary excretion of albumin. This study contributes to a growing literature that suggests that overt albuminuria does not always precede a significant loss of GFR in the setting of diabetes and that measuring albuminuria alone does not fully capture the scope of early diabetic kidney disease (6–8). Instead, albuminuria and GFR loss may represent complementary, if overlapping, manifestations of kidney damage.

This supposition raises important questions. Are the underlying pathophysiologic processes and clinical risk factors of

albuminuria and loss of GFR different in the early stages of diabetic kidney disease? How do albuminuria and loss of GFR each affect prognosis in terms of future decline in kidney function and the concurrent increasing risk for other complications such as cardiovascular disease? In particular, can early loss of GFR be slowed or even reversed, as we now believe microalbuminuria can regress? Do albuminuria and loss of GFR warrant different targeted therapeutic interventions? As Perkins *et al.* suggest, might successful treatment to improve values for glycemia, BP, and lipid concentrations reduce the rate of decline or halt the fall in GFR? To answer these questions, we are in critical need of a reliable marker of early GFR loss.

The development of new biomarkers in nephrology has lagged behind that in other disciplines. For instance, whereas we now can diagnose with great specificity and sensitivity myocardial infarction with troponin concentrations in serum, we can only crudely estimate GFR using serum creatinine concentrations. The National Kidney Disease Education Program (<http://www.nkdep.nih.gov>) and the National Kidney Foundation (9) now recommend the use of estimating equations to improve the diagnostic accuracy of serum creatinine. These recommendations constitute a large step forward, with GFR most often estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation (10). This works reasonably well for patients whose eGFR is < 60 ml/min per 1.73 m^2 . However, the lack of accuracy of the MDRD equation above an eGFR of 60 ml/min per 1.73 m^2 constitutes a significant limitation to its application in many clinical scenarios, including early diabetic kidney disease. Even a careful protocol to standardize creatinine measurements across all instruments in clinical laboratories and likely a more consistently applied MDRD equation (11) are still unlikely to permit sufficient accuracy in the “subnormal” range of kidney function (*i.e.*, GFR from 60 to 90 ml/min per 1.73 m^2 or higher). GFR estimates that are based on serum creatinine concentration are further limited by variation in creatinine production on the basis of age, gender, race, and body composition. Therefore, while continuing to encourage the use of creatinine-based estimating equations, the nephrology community should eagerly seek other methods to measure or better estimate GFR.

Measurement of serum cystatin C concentration has attracted increasing attention as an alternative method to assess GFR in clinical medicine. Most reports suggest that the relationship of

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cystatin C with GFR as measured using clearance of radiolabeled or unlabeled compounds does not depend on age or gender (12). Moreover, serum cystatin C may more reliably detect differences in GFR when GFR is >60 ml/min per 1.73 m² (13–16). When cystatin C concentrations are expressed as 100/cystatin C or transformed using prediction equations, they have the potential to improve the accuracy of eGFR (17). However, most studies that have assessed serum cystatin C as a measure of GFR have been cross-sectional in nature, and longitudinal studies are needed to define further the potential role of cystatin C in clinical care. In a previous issue of *JASN*, Perkins *et al.* (18) reported the first such longitudinal study. Changes over time in GFR (measured by clearance of iothalamate), serum creatinine eGFR, and cystatin C eGFR were compared among 30 Pima Indians with a mean baseline GFR 153 ml/min per 1.73 m². The change in 100/cystatin C correlated with the change in iothalamate-GFR more accurately than did the change in eGFR as calculated from serum creatinine.

We agree with Perkins *et al.* and with the National Kidney Disease Education Program that improved measurements/estimates of GFR must become a component of routine clinical care for people with diabetes. Serum cystatin C is an excellent candidate for this measurement. As stated previously (19), the much greater costs of cystatin C assays currently reduce their application in clinical medicine. However, when cystatin C is added to the menus of random access analyzers that are ubiquitous in clinical laboratories, it may be more readily used in general medical practice and in clinical nephrology.

The study by Perkins *et al.* in this issue of *JASN* was restricted to people with type 1 diabetes. However, it is important to note that early loss of GFR also has important consequences in the general population (20). Cystatin C shows promise as a valuable tool to describe the pathophysiologic, diagnostic, prognostic, and therapeutic implications of GFR loss, independent of and together with albuminuria, among people with and without diabetes.

Disclosures

None.

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See the related article, "Microalbuminuria and the Risk for Early Progressive Renal Function Decline Type 1 Diabetes," on pages 1353–1361.