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Structural Predictors of Renal Function Decline

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Author
Nicholas, Susanne B

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Susanne B. Nicholas

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The diagnosis of CKD is typically made on the basis of interpretations of reduced renal function (using the Modification of Diet in Renal Disease eGFR<60 ml/min per 1.73m^2), kidney damage, the presence of small kidneys on imaging, or oliguria (1). The natural decline in renal function in adults (aged >30–40 years) is usually defined by a decrease in eGFR of approximately 1 ml/min per 1.73m^2 per year. Data accumulated from numerous longitudinal studies indicate that there is actually a wide range in the decline of renal function, between 0.36 and 1.21 ml/min per 1.73m^2 per year for healthy individuals (2–5). In CKD, the rate of renal function decline may vary even more widely, affected by several factors such as the underlying population, the CKD cause, the presence of albuminuria/proteinuria, comorbidities (0.05–1.71 ml/min per 1.73m^2) (2,3,6), and age (0.8–2.7 ml/min per 1.73m^2 in older adults) (7,8). In order to assess the rate of progression of CKD, several of these parameters should be considered and eGFR and albuminuria should be checked at least once a year, and probably more frequently in patients at higher risk (1). Owing to a paucity of relevant studies, there is no definitive policy to guide the actual frequency of these measurements relative to specific risk categories that could otherwise facilitate targeted strategies and prevent adverse outcomes, such as ESRD and death (1).

The implications of regular surveillance may be even more important and germane to patients with diabetic kidney disease (DKD). Diabetes continues to be the most common cause of CKD and ESRD and ethnic minorities; especially American Indians, Hispanics, black Americans, and Pacific Islanders are at significantly higher risk of CKD progression and premature mortality (9,10). The clinical syndrome of diabetic nephropathy, initially defined in the mid-1900s, was described by "intercapillary" or nodular glomerulosclerosis (Kimmelstiel–Wilson nodule) in patients with long-standing diabetes (usually >20 years), persistent albuminuria (>300 mg/d on at least two occasions over 3–6 months), hypertension, retinopathy, and progressive loss of renal function (11,12). This definition was later accompanied by the classic five stages of the disease natural history: Stage I, hyperfiltration with glomerular hypertrophy and transient albuminuria; Stage II, silent phase with normalization of GFR and albumin excretion rate, accompanied by thickened glomerular basement membrane (GBM) and an expanded mesangium defined by increased mesangial fractional volume per glomerulus; Stage III, incipient nephropathy with persistent microalbuminuria; Stage IV, overt nephropathy with worsening albuminuria (to macroalbuminuria) and retinopathy, increasing blood pressure, and declining renal function; and finally Stage V, variable GFR loss toward ESRD, characteristically occurring over 25–30 years, but commonly pre-empted by death (13). Although this model was based primarily on information from patients with type 1 diabetes (14,15), it was routinely also applied to patients with type 2 diabetes.

Notably, this archetype has undergone significant modification over the last several years from new knowledge gleaned from clinical observations, experience with standard therapies, prospective studies, and detailed morphometric analyses of kidney biopsies. Clear differences beyond the epidemiology and clinical presentation between type 1 and type 2 diabetes are now well recognized. Thus, the new term DKD appropriately reflects the observed structural and clinical heterogeneity of the disease, and especially the discordance between decline in renal function and albuminuria (16) that was not previously fully appreciated.

In 1996, Fioretto *et al.* summarized observations from research kidney biopsies from microalbuminuric patients with type 2 diabetes (17). Three categories of structural pathology and prognostic implications were described: patients in Category I had normal to near normal renal structure, and this was seen in 35% of those with microalbuminuria and 10% with proteinuria; patients in Category II had "typical" diabetic nephropathology (as in type 1), seen in 30% of those with microalbuminuria and 55% with proteinuria. Significant proliferative retinopathy, longer diabetes duration, worse metabolic control, and faster decline in renal function were common features among patients in this category. Patients in Category III showed atypical patterns of renal injury with absent or only mild diabetic glomerular lesions, seen in 35% of those with microalbuminuria and proteinuria, but all had worse metabolic control. The study suggested that knowledge of the underlying renal structure may potentially intensify therapies for disease stabilization or reduction in renal function. Later, in 2010, the Research Committee of the Renal Pathology Society proposed a new classification, on the basis of biopsies from patients with both type 1 and type 2 diabetes, into four classes (18): Class I, mild or nonspecific light microscopy– and electron microscopy–proven GBM thickening; Class IIa, mild mesangial expansion; Class IIb, severe mesangial expansion; Class

Department of Medicine, Divisions of Nephrology and Endocrinology, David Geffen School of Medicine at University of California, Los Angeles, California

Correspondence: Dr. Susanne B. Nicholas, 900 Veteran Avenue, Suite 24-130, Los Angeles, CA 90045. Email: sunicholas@mednet.ucla.edu

III, nodular sclerosis; and Class IV, advanced diabetic glomerulosclerosis. The new system, which also referenced the degree of interstitial fibrosis, interstitial inflammation, and vascular lesions, was intended to provide clinicians and researchers a consensus on staging and criteria to discriminate lesions with different degrees of severity and prognostic value. This accumulation of observations has begun to prompt the prospect of more frequent kidney biopsies as a tool to direct timing and targeting of standard/novel therapies to improve patient outcome in DKD (19).

However, there is a noticeable dearth of studies of kidney biopsies that can effectively link renal structure with loss of function, especially in patients with type 2 diabetes at higher risk of DKD progression. Because the rate of renal function decline is strongly associated with mortality (20), and the rapid loss of renal function (*i.e.*, >3 ml/min per 1.73m^2 per year [1]) is associated with a significantly higher risk of coronary heart disease and all-cause mortality (21), particularly in specific patient populations (22), it would be prudent to consider including rate of renal function decline as part of the diagnostic criteria in order to optimize patient care.

The study by Fufaa *et al.* (23) is a timely and relevant paper that investigated the association between detailed quantitative morphometric analyses of glomerular structures and loss of renal function. In essence, the study demonstrated that this type of rigorous investigation may uncover parameters that predict the loss of renal function in a high-risk cohort. The observational study was performed in obese, nonhypertensive Pima Indians (n=111) with type 2 diabetes in whom serial biopsies and annual iothalamate-clearance GFR were obtained over a median of 6.6 years. The analysis of research biopsies was very rigorous in nature and quantified mean glomerular volume, GBM width, cortical interstitial fractional volume, mesangial fractional volume per glomerulus, glomerular filtration surface density, total filtration surface per glomerulus, number of nonpodocyte cells (*i.e.*, endothelial and mesangial cells) per glomerulus, number of podocytes per glomerulus, podocyte foot process width, percentage podocyte detachment, and percentage of normally fenestrated endothelium, by a single blinded investigator. The results of the study showed that many of the classic glomerular features of DKD were present at baseline, in addition to reduced endothelial fenestrations in those with increased albuminuria, and increased interstitial volume in those with macroalbuminuria. At baseline, approximately 13% had GFR<90 ml/min per 1.73m^2 and also had more globally sclerosed glomeruli and interstitial fractional volume, although the majority (87%) of patients had GFR>90 ml/min per 1.73m^2, and those (37%) with hyperfiltration (GFR≥154 ml/min per 1.73m^2) had higher total glomerular filtration surface per glomerulus and podocyte number per glomerulus. Interestingly, 55% of the cohort who developed renal function loss also had hyperfiltration, and those with higher mean baseline GFR were also progressors (≥40% decline) compared with the nonprogressors. Indeed, hyperfiltration in type 1 diabetes is believed to predispose to renal function decline, and has been deemed an independent predictor of micro- and macroalbuminuria in type 1 diabetes (24), but this still remains to be proven. Several glomerular features (mesangial expansion, percentage global sclerosis, nonpodocyte cell number per glomerulus, GBM width, mean glomerular size, podocyte foot process width, lower glomerular filtration surface density, and fewer endothelial fenestrations), were associated with renal function loss, and the feature that predicted loss in renal function was podocyte process width. Also, the predictive value of structural parameters was not related to the use of a renin-angiotensin-system inhibitor, even though 55% of patients were on such an inhibitor.

There are several strengths to the study. In particular, American Indians have a higher prevalence of CKD and ESRD versus whites (25) and were a suitable cohort for this type of study; all participants had prolonged diabetes (16±6 years); serial research biopsies provided sufficient tissue for extensive morphometric analyses by validated, unbiased stereologic methods; and serial HPLC–iothalamate clearance provided accurate measures of renal function. Of note, the authors appropriately eliminated blood pressure in the analysis, which could have confounded the effect on structural changes. The study, however, was not designed to assess the link between albuminuria and renal function decline or the effect of interventional strategies.

This is not the first study to show the predictive value of kidney biopsy in type 2 diabetes, but this study provides support for the clinical role of robust, longitudinal analyses in ethnic minority populations at disproportionately high risk of DKD progression. These kinds of studies could provide useful information to enable: identification of specific cell types that could be targeted for therapy; risk stratification; discovery and validation of novel biomarkers; and genetic studies to correlate genes with specific glomerular pathologies, and test the efficacy of new treatments, as well as promote personalized care. Currently, patients with diabetes undergo diagnostic kidney biopsy in the presence of an atypical clinical course and to date there is no clinical indication for kidney biopsy that would provide prognostic information. Clearly, despite the last approximately 80 years of knowledge of DKD, there is still much to garner.

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Disclosures

The author is on the board of directors of the National Kidney Foundation and has no other disclosures to declare.

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