# The Changing Landscape of Diabetic Kidney Disease: New Reflections on Phenotype, Classification, and Disease Progression to Influence Future Investigative Studies and Therapeutic Trials

Diabetic kidney disease (DKD) occurs in approximately 1/3 of adults with diabetes. Growth of CKD has increased in parallel with rising prevalence rates of diabetes. This growth has occurred irrespective of the increased use of glucose-lowering medications and antihypertensive therapy, including the use of renin-angiotensin-aldosterone system (RAAS) inhibitors.[1] The adjusted increase in DKD prevalence was 34% from 1988 to 2004 through 2005 to 2008 despite reciprocal decreases in mean hemoglobin A1c, systolic and diastolic blood pressures, and low-density lipoprotein cholesterol levels over the same time period. The incidence rate of ESRD from diabetes, although high, appears to have declined slightly as of 2011, although temporal trends in ESRD incidence differ by age and race/ethnicity.[2]

As reviewed by Professor Marshall in this issue, the traditional model of type 1 diabetic kidney disease (T1DKD) progression has evolved. Longitudinal studies of individuals with type 1 diabetes (T1D), who were initially followed starting in the 1930s, demonstrated that approximately 40% developed persistent proteinuria with a maximum incidence after approximately 15 years and a maximum prevalence after 20 to 25 years duration of T1D. Death occurred in half within 10 years of developing proteinuria. ESRD accounted for 2/3 of all deaths.[3] A decline in the cumulative incidence of proteinuria and time to ESRD observed in cohort studies over the past 3 decades appears to have occurred in part as a result of improvements in blood pressure control, RAAS inhibitor use (as discussed by Yamout and colleagues), and lipid and glycemic management. Optimistically, in the Diabetes Control and Complications Trial (DCCT) and its follow-up study the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, the cumulative incidence of an estimated glomerular filtration rate (eGFR) less than 60 mL/minute per 1.73 $m^2$ was 5.5% in those assigned to conventional therapy and 2.0% among those assigned to intensive therapy with a low incidence rate of ESRD.[4] Improved outcomes were also apparent in the Steno Diabetes Center study in which 25% of T1DKD patients with macroalbuminuria reached ESRD during 10 years of follow-up, although death occurred in 30% of patients and with almost half of these as a result of cardiovascular causes.[5] In this issue, Harjutsalo and Groop comprehensively review the epidemiology of DKD. Pálsson and Patel review new evidence for the substantial burden of cardiovascular disease in the diabetic population with kidney disease.

Even so, in the case of T1DKD, the risk and occurrence of ESRD and pre-ESRD mortality remain unacceptably high as revealed by other cohort studies. The timing of ESRD occurrence may have been postponed to a more prolonged duration of diabetes and advanced age as a result of renoprotective and antihypertensive therapies, but the implication is that the current emphasis of treatment directed at the prevention or reduction in albuminuria may not be sufficient.[6] In the Finnish Diabetic Nephropathy study, 36% of T1DKD patients with macroalbuminuria and a median duration of diabetes of 29 years developed ESRD during a median follow-up of 9.9 years (incidence of 5.1 per 100 person-years), whereas 9.5% of patients died without developing ESRD.[7] Likewise, the ESRD incidence was 5.8 patients per 100 person-years in the Joslin Clinic study with a cumulative pre-ESRD death rate at 10 years of 6.9%; 2/3 of deaths were attributed to cardiovascular disease.[8]

Particularly for T1DKD, but applied also to T2DKD, the classical paradigm describing the natural history of DKD from the 1980s described a fairly linear, predictable progression marked by stages of glomerular hyperfiltration, normal glomerular filtration rate (GFR) with normoalbuminuria, progressive albuminuria and persistent proteinuria, and subsequent declining GFR leading to ESRD. It subsequently has become increasingly evident that this model of DKD is less than adequate. Contrary to the classical paradigm, there is significant variability in the kidney phenotype of individuals with DKD. This improved understanding of DKD has complicated the investigation and validation of study findings. Variability among T1DKD cohorts became evident in large population-based cohort studies published in the 1990s. Phenotypic variability may account in part for the very modest reproducibility characterizing genetic studies regardless of study design despite the strong familial aggregation and differing geographical prevalence observed for DKD.

The basic clinical traits of microalbuminuria, proteinuria, and changes in GFR appear to represent phenotypic characteristics with much less interdependence than previously believed for DKD. Increased urine albumin


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excretion remains a good predictor of declining kidney function; however, this phenotypic picture is complex. Microalbuminuria may regress to normal urine albumin excretion instead of progressing to more significant proteinuria in the absence of RAAS inhibitor use, as exemplified by a 40% 10-year cumulative incidence in DCCT/EDIC,[9] or it may remain stable. Overall, such an event appears to occur at least as often as (if not more often than) progression to macroalbuminuria in T1D (35-64%) and in type 2 diabetes (T2D; 21-51%).[10] Moreover, declines in GFR occur in the absence of substantive increases in urinary albumin excretion, suggesting that increased urine albumin excretion may not represent an obligatory step preceding GFR decline in T1D (13-24%) and T2D (35-73%).[10] In the DCCT and EDIC studies, 90% and 19% of patients with T1D with a history of microalbuminuria and macroalbuminuria reverted to having normal urine albumin excretion on at least 1 visit, respectively.[11] Moreover, 24% of patients with a sustained and reduced eGFR (<60 mL/minute per 1.73 $m^2$) did not have a preceding history of increased urine albumin excretion. Likewise, 26% of participants in the Pittsburgh Epidemiology of Diabetes Complications study with type 1 diabetes who developed reduced eGFR did not have preceding micro- or macroalbuminuria in the absence of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy, whereas all patients who progressed to ESRD previously had increased urine albumin excretion.[12] In patients exhibiting less severe kidney dysfunction, early renal function decline (loss of cystatin C-GFR more than −3.3% per year) occurred in 9% with normal urine albumin excretion vs 31% with microalbuminuria over 8 to 12 years in the Joslin Kidney study, whereas regression of microalbuminuria was associated with decreased risk of its occurrence.[13] Early renal function decline and the development of microalbuminuria appear to be distinct features in a subset of individuals, with proteinuria not required for the development of DKD.[14]

The discordance between progression of urine albumin excretion and GFR decline in DKD is also demonstrated by the substantial proportion of T2D patients who develop reduced eGFR despite having normal urinary albumin excretion rates—at least in part reflecting a greater clinical heterogeneity, macrovascular disease, and complexity of underlying kidney lesions.[15] In cross-sectional studies, an absence of macroalbuminuria occurs in a substantial fraction of T2D patients with a GFR less than 60 mL/minute per 1.73 $m^2$—33% in the Third National Health and Nutrition Examination Study[16] and 63.6%, excluding those on angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy, in the Renal Insufficiency And Cardiovascular Events study.[17] In the U.K. Prospective Diabetes Study 74 cohort, 51% of patients developing kidney insufficiency over a median of 15 years after T2D diagnosis did not have preceding macroalbuminuria, whereas 16% of patients developed microalbuminuria or macroalbuminuria subsequent to developing a GFR less than 60 mL/minute per 1.73 $m^2$.[18] Here also, microalbuminuria in T2DKD, as in T1DKD, may regress, persist, or progress (respectively 31%, 38%, and 31%) as exhibited by 151 T2D patients with baseline microalbuminuria in the Steno-2 study.[19]

Together these studies suggest that changes in increased urine albumin excretion in T1DKD and T2DKD may represent very dynamic patterns of injury by comparison to the kidney injury associated with GFR decline. This paradigm shift implies that each of these traits may reflect a different mosaic of underlying genetic, glycemic, hemodynamic, and environmental determinants, and that the relationships between these traits are significantly more complicated than can be predicted under an assumption of linear progression. In this issue, Thomas reviews the concept of "metabolic memory," while exploring the potential utility of early glycemic control and therapeutic interventions to delay and minimize the onset of DKD. Such a shift in thought also reveals an additional level of complexity inherent in designing and interpreting data arising from diabetic subpopulations classified by the presence of increased urine albumin excretion and/or decreased GFR, and it may contribute in part to the observed failure of RAAS blockade to appreciably affect GFR outcomes in some studies. The onset of proteinuria appears to have been delayed in more recent studies of DKD patients, possibly as an effect of improved glycemic, blood pressure, and therapeutic management.[3,6] Thus, the importance of assessing GFR and increased urine albumin excretion to detect and monitor kidney disease in patients with diabetes deserves more emphasis.

The phenotypic heterogeneity of DKD is further revealed by histologic correlates, perhaps best exemplified in T2DKD. Clinically indicated kidney biopsy series of T2DKD patients, which are selection-biased toward atypical presentations, have demonstrated classical diabetic lesions identical to those well described in T1DKD[15] in 1/3 of biopsies. Histologically, the pattern of kidney lesions in T1DKD and T2DKD overlap, but they are clearly distinct. One biopsy series in T2DKD patients with widely varying levels of proteinuria and GFR identified classical diabetic changes in 37% of biopsies, with severe interstitial disease, tubular atrophy, arteriosclerosis, and less arteriolar hyalinosis in another 30%. The remaining 33% of biopsies revealed mixed kidney lesions combining diabetic lesions and superimposed nondiabetic glomerular disease.[20] Likewise, a recent large retrospective analysis of kidney biopsies performed in 611 T2D and T1D patients during 2011 confirmed the degree of this heterogeneity, with 37% patients exhibiting DKD alone, 27% exhibiting combined DKD and nondiabetic kidney disease, and 36% exhibiting nondiabetic kidney