Burden of Proof—When Is Kidney Disease Attributable to Diabetes?

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Diabetic kidney disease (DKD) refers to CKD that is caused by diabetes. Although kidney biopsy is required for a definitive diagnosis, it is thought that careful screening of patients with diabetes can identify many of those with DKD without the need for kidney biopsy (1). This screening includes measurement of urine albumin excretion and calculation of eGFR. In the absence of another kidney disease, the finding of persistent albuminuria, persistent reduction in the GFR to <60 ml/min per 1.73 m^2, or both in a patient with diabetes is generally considered sufficient for a diagnosis of DKD, particularly in those with diabetes of long duration or in the presence of diabetic retinopathy.

More than 30 million people in the United States have diabetes. Worldwide, the number of people with diabetes has doubled in the past 20 years, and the International Diabetes Federation estimates that, in 2015, there were 415 million adults ages 20–79 years old with diabetes (2). Improved health care and living standards have expanded the elderly population, which is at considerable risk for type 2 diabetes and carries a high burden of comorbid conditions that may affect the kidneys. A decline in physical activity and preference for calorie-dense foods have prompted a dramatic rise in obesity at all ages, which has contributed to an increase in type 2 diabetes in children, adolescents, and young adults (3) as well as an earlier onset of type 1 diabetes. The prevalence of obesity among children and adolescents has recently stabilized in some parts of the world, but severe obesity in children is becoming more frequent, particularly in the United States (4), and may greatly amplify the risk of type 2 diabetes in youth. Adverse health effects of exposure to diabetes *in utero* are also fueling the rise in obesity and type 2 diabetes in the young, and 16% of live births worldwide are now affected by hyperglycemia in pregnancy (2). Of concern, the course of DKD in youth-onset type 2 diabetes is more aggressive than in type 1 diabetes (5) and may lead to increasing rates of ESRD in midlife.

On a positive note, improvements in patient management and the availability of more effective medicines have led to a reduction in the frequency of major complications of diabetes in recent years, with the greatest reductions observed for macrovascular complications, although reductions in microvascular complications, including DKD, have also been observed (6). The incidence of ESRD attributable to diabetes in the United States plateaued in the late 1990s and is now declining modestly, particularly in older age groups and certain racial/ethnic groups, presumably in response to treatments that slow the progression of DKD.

Changes in the populations at risk for diabetes, which increasingly include the young and favor certain racial/ethnic groups, along with the introduction of effective medicines that modulate GFR and reduce the urine excretion of albumin, even in the setting of established kidney disease, are affecting the clinical manifestations of kidney disease among those with diabetes in the United States (7). Traditional markers once considered reliable indicators of kidney disease are no longer as helpful for identifying early disease, establishing its underlying cause, and assessing its likelihood of progression. Nevertheless, the available evidence suggests that diabetes remains a major determinant of kidney disease in the United States and worldwide.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Zelnick *et al.* (8) used data from the National Health and Nutrition Examination Survey (NHANES) to determine the extent to which the clinical manifestations of CKD in persons with diabetes could be attributed to diabetes or were attributable to other factors, including age, sex, race/ethnicity, and hypertension. Data from three NHANES cycles, 2009–2010, 2011–2012, and 2013–2014, were analyzed. Diabetes mellitus was defined as the use of a glucose-lowering agent and/or hemoglobin A1c >6.5%. Albuminuria was defined as a urine albumin-to-creatinine ratio (ACR) ≥30 mg/g, and macroalbuminuria was defined as an ACR≥300 mg/g from a spot urine sample. eGFR was derived using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation. Persistence of albuminuria and eGFR were assessed in subsets of participants who underwent repeated testing, and an estimate of the prevalence of persistence of each of these CKD outcomes was used in subsequent modeling. CKD was defined as an ACR≥30 or ≥300 mg/g or an eGFR <60 or <30 ml/min per 1.73 m^2. Any CKD was defined as an ACR≥30 mg/g, an eGFR<60 ml/min per 1.73 m^2, or both. The extent to which each CKD outcome was attributable to diabetes in the study participants was computed after adjusting for age, sex, and race/ethnicity and additionally adjusted for measures of BP to disaggregate the effects of these

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covariates from the effect of diabetes *per se*. Population-attributable risk was then computed among all adults in the United States to determine the total population prevalence of each CKD outcome that was attributable to diabetes after accounting for age, sex, and race/ethnicity.

Of the 15,675 participating adults included in this analysis, 2279 had diabetes, and 13,396 did not. Those with diabetes were older, more likely to be black or Mexican-American, and more likely to have a history of hypertension. The prevalence of each CKD outcome was substantially higher in participants with diabetes than in those without, and after adjustment for the prespecified confounders, the prevalence ratios were attenuated but remained highly statistically significant. Among participants with diabetes, 51% of any CKD was attributable to diabetes after adjustment for these confounders. When standardized to account for age, sex, and race/ethnicity, 24% of the total United States population prevalence of any CKD was attributable to diabetes.

This study used national survey data to illustrate that diabetes is strongly associated with albuminuria and reduced eGFR, even after accounting for other factors, including age, sex, race/ethnicity, and BP, each of which is also known to influence these outcomes. Moreover, it confirms that a sizeable proportion of CKD in the United States is attributable to diabetes. Although this conclusion is not new, this study adds further urgency to current efforts to characterize the underlying mechanisms of DKD, identify new therapies to target these mechanisms, and discover new biomarkers that will more accurately reflect whether a patient with diabetes has DKD or another type of CKD and if it is likely to progress (9). To do so, however, requires access to kidney tissue in informative populations, which is a principal goal of the Kidney Precision Medicine Project currently underway with support from the National Institute of Diabetes and Digestive and Kidney Diseases. When targeting the mechanisms of DKD, kidney biopsies must be performed in those most likely to have DKD rather than the traditional clinical biopsy, which is typically performed to rule out a nondiabetic cause of kidney disease in a patient with diabetes.

As noted by the study investigators, the excess risk of CKD attributable to diabetes could be due to direct causal effects of diabetes, other causal mechanisms related to diabetes, treatments associated with diabetes, or confounding by other characteristics more common in diabetes. One such confounder is obesity. Although obesity-related glomerulopathy may represent a distinct entity from DKD, obesity is largely responsible for the increase in diabetes prevalence worldwide, and similarities in underlying mechanisms of obesity-related CKD and DKD suggest that treatments targeting obesity-related CKD may slow the progression of kidney disease in patients with diabetes (10).

Finally, the burden of CKD attributable to diabetes is not uniformly distributed in the population, and studies to identify new mechanisms, treatments, or biomarkers should include patients at greatest risk, not just those easiest to recruit for invasive clinical studies. Identifying mechanisms leading to the more aggressive course of DKD among people diagnosed with type 2 diabetes in youth (5), for example, requires enrollment of young people, often from minority or disadvantaged groups. Ultimately, the burden of proof that CKD is attributable to diabetes rests with patients, who accept the risks associated with this much-needed research in the hope of benefitting themselves and future generations, and the investigators, who perform these studies in the hope of establishing the underlying mechanisms of DKD and providing new and more effective therapies to treat it. The study by Zelnick *et al.* (8) reminds us of the urgency and importance of this work.

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Disclosures

None.

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