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Diabetic Kidney Disease: The "Silent" Majority?

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Diabetes is one of the biggest health care challenges of the 21st century. It affects >422 million people worldwide and is the leading cause of chronic kidney disease and end-stage kidney disease worldwide.[1] In the United States, 47% of incident end-stage kidney disease cases are attributable to diabetes, whereas in Singapore and Malaysia, that number exceeds 65%.[1] Unfortunately, the burden of diabetic kidney disease (DKD) is increasing. The average yearly increase in the incidence of end-stage kidney disease owing to diabetes is 3% in the United States and exceeds 10% in the Republic of Korea.[1]

The pathogenesis of DKD is complex with many interacting pathomechanisms described, including the deleterious effects of hyperglycemia-induced advanced glycation end-products, glomerular hypertension, kidney hypoxia, dysregulation of podocyte-endothelial crosstalk, podocyte loss, and inflammation.[2] Our understanding of DKD has evolved from the original description of Morgensen when it was believed that DKD is a disease that starts with kidney hyperfiltration and progresses to stages of increasing levels of albuminuria, ultimately leading to kidney dysfunction and culminating in end-stage kidney disease. This evolution in our understanding has been fueled by several observations. For example, many patients with DKD present with a sustained reduction in estimated glomerular filtration rate without albuminuria.[3] Furthermore, albuminuria does not necessarily follow a linear path of progressive increase and can regress in many patients,[4] making albuminuria an unreliable means of diagnosing DKD.

The kidney biopsy is the gold standard for diagnosing DKD; however, it is seldom performed in routine clinical practice unless there is concern for an alternative cause of kidney disease or if the disease presentation has atypical features, such as nephrotic-range proteinuria or rapidly declining kidney function. The relationship between histologic and clinical manifestations (such as proteinuria level) of DKD is not well established; however, there is accumulating evidence that suggests histologic changes of DKD begin early in the disease course and precede clinical manifestations. For example, thickening of the glomerular basement membrane, which occurs owing to extracellular matrix deposition, can be detected within 2.5 years of disease onset in type 1 diabetes mellitus, whereas mesangial expansion can be found after 5 to 7 years of diagnosis.[5] In addition, the progression of those lesions over time is not uniform.[5] Despite that, by the time clinical manifestations are observed, mesangial expansion and thickening of the glomerular basement membrane are almost universal.[5] Thus, it is likely that the prevalence of DKD is underappreciated when only clinical manifestations are used for diagnosis. The study by Sasaki *et al.*[6] published in this issue of *KI Reports* is apropos as it helps to identify the burden of clinically silent DKD. In their study, Sasaki *et al.*[6] used the Hisayama cohort, a longitudinal study of cardiovascular disease in a Japanese population. In this study, patients had routine clinical examinations, and on their death, most had an autopsy. The investigators identified a subgroup of 106 patients with diabetes whose kidneys were evaluated histologically at the time of death. All patients had a urine albumin-to-creatinine ratio (ACR) measured within 6 years of death. The patients were split into 3 groups based on their level of albuminuria (no albuminuria, ACR 30–300, or ACR >300), and the relationship between albuminuria levels and severity of histologic features according to the Renal Pathology Society scoring system was evaluated. The study provided several new insights. More than 50% of patients without albuminuria had class II or worse glomerular lesions. This observation was preserved when the analysis was restricted to patients whose ACR

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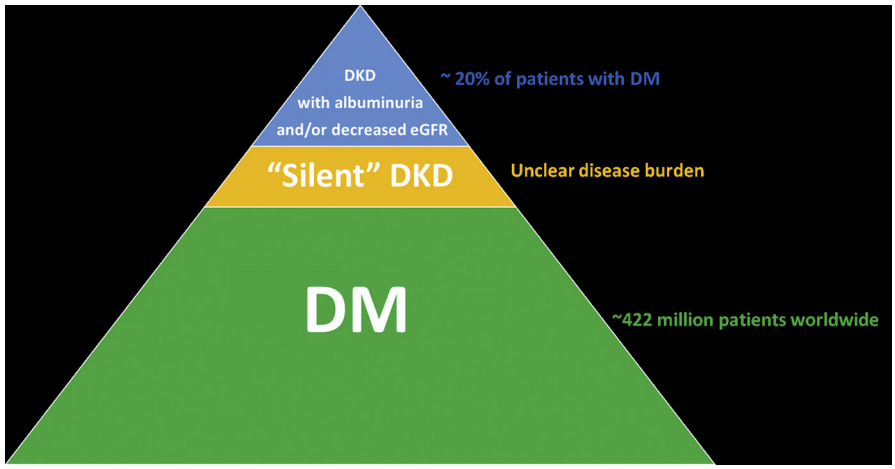

Figure 1. Current understanding of the burden of DKD. DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate.

measurement was within 2 or 3 years of autopsy. In addition, the frequency and severity of histologic lesions observed in DKD (such as glomerulosclerosis and mesangial expansion) increased as albuminuria increased, even at a "physiologic" ACR of <30, suggesting DKD is a continuum that starts before development of albuminuria. The findings from this study replicate findings from a study of 168 Dutch patients with type 1 or 2 diabetes, 106 of whom had histologic changes of DKD despite the absence of clinical manifestations.[7]

The study by Sasaki *et al.*[6] had some limitations. First, electron microscopic examination of the kidney tissue was not performed; thus, the prevalence of early diabetic changes (such as thickening of the glomerular basement membrane) could not be determined. Second, there was a significant time lag between the measurement of the ACR and kidney histology evaluation; thus, it is possible that patients in the no-albuminuria group actually had albuminuria at the time of their demise. Nonetheless, the observations of the authors were consistent when they restricted their analysis to patients who had ACRs measured <2 or 3 years from the time of biopsy; thus, it is unlikely that this time lag had a significant influence on the observed results.

It seems that we are missing a large cohort of clinically silent DKD (Figure 1). Nevertheless, it is not clear whether earlier identification of those patients and subsequent initiation of currently available therapies would alter their disease trajectory. For example, despite the benefit of inhibition of the renin-angiotensin-aldosterone system in proteinuric DKD, limited data revealing their benefit exist for nonproteinuric DKD. Nevertheless, the recent success of sodium-glucose co-transporter–2 inhibitors in DKD provides hope that these treatments can slow DKD even early in the disease course. Sodium-glucose co-transporter–2 inhibitors can mitigate many of the pathogenic mechanisms that underlie DKD, and their therapeutic benefits are not only limited to their favorable effects on the classical pathomechanisms of DKD, such as hyperglycemia, hypertension, and tubuloglomerular feedback, but also extend to decreasing kidney hypoxia, podocyte loss, lipotoxicity, inflammation, and endothelial dysfunction.[2] An insight in the potential benefit of sodium-glucose co-transporter inhibitors in preclinical disease can be inferred from clinical trials. The EMPA-REG OUTCOMES trial, which enrolled patients with diabetes with established cardiovascular disease, revealed consistent benefits on renal outcomes even in patients with an estimated glomerular filtration rate >90 ml/min per 1.73 m^2 or those without albuminuria.[8] The CANVAS program revealed benefit of the sodium-glucose co-transporter inhibitor canagliflozin in stabilizing estimated glomerular filtration rate slope for patients with no albuminuria.[9] Furthermore, canagliflozin-treated patients had a lower risk for new-onset microalbuminuria, suggesting it is beneficial early on in the disease course. That being said, most patients enrolled in those trials were receiving renin-angiotensin-aldosterone system blockers; thus, the effect of sodium-glucose co-transporter–2 inhibitor in patients not receiving renin-angiotensin-aldosterone system blockade is not well established. Moreover, those were trials that were primarily designed to evaluate cardiovascular outcomes, and thus far, kidney-centric trials evaluating the utility of sodium-glucose co-transporter–2 inhibitor in early DKD (i.e., patients with diabetes with estimated glomerular filtration rate >90 and without albuminuria) have not been performed. A clinical trial revealing benefit in such a population can potentially be paradigm changing and shift clinical practice to attempt early identification of DKD by kidney biopsy before overt clinical signs of DKD. In the future, early diagnosis of DKD may potentially be done using noninvasive biomarkers. Clinical studies using multiomics characterization of the kidney tissue of patients with diabetes, such as the Transformative Research in Diabetic Nephropathy study, may help bring such biomarker(s) to reality.

DISCLOSURE

All the authors declared no competing interests.

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