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Editorial Comment

EDITORIAL COMMENT

Diagnosis 101: diabetic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) attributed to diabetes occurs in 20%–40% of patients with diabetes mellitus. Diabetic kidney disease (DKD) is recognized as the most common cause of end-stage kidney disease in the USA and most Western countries. For quite some time, it has been recognized that treatments based on inhibition of the renin-angiotensin system (RAS) can reduce the rates of cardiovascular morbidity and mortality in patients with DKD. Recently however, several novel agents, namely sodium-glucose co-transporter 2 inhibitors, dipeptidyl peptidase 4 inhibitors and glucagon-like peptide-1 receptor agonists, were demonstrated to not only improve glycemic control but also to improve cardiovascular and renal outcomes. Another agent, a nonsteroidal mineralocorticoid antagonist, has also been shown to have cardiorenal benefits in patients with DKD. With such new developments, one would expect that it would eventually translate into further slowing CKD progression in the DKD population, provided that patients are diagnosed appropriately and in a timely manner. In this study, the authors attempt to investigate real-world data, looking at how well providers are establishing the diagnosis of DKD and its potential implications.

Keywords: albuminuria, CKD, diabetic kidney disease, GFR, type 2 diabetes

> "A correct diagnosis is three fourths the remedy."
> Mahatma Gandhi

Chronic kidney disease (CKD) attributed to diabetes occurs in 20%–40% of patients with diabetes mellitus (DM) [1]. While diabetic kidney disease (DKD) typically develops 10 years following a diagnosis of type 1 DM, with regard to type 2 DM, it may already be present at the time one makes a diagnosis. DKD is recognized as the most common cause of end-stage kidney disease (ESKD) in the USA [2] and most Western countries.

DKD is usually a clinical diagnosis made on the basis of reduced estimated glomerular filtration rate (eGFR) and persistently increased albuminuria (>300 mg/g creatinine). The typical clinical presentation of DKD is in patients with a prolonged duration of diabetes (>10 years in type 1 DM), the presence of retinopathy, albuminuria without hematuria and gradual and progressive loss of GFR. However, in more recent years, the heterogeneity in clinical presentation has become more evident [3].

Screening for and early diagnosis of DKD may lead to early initiation of therapy that, in turn, may help delay the progression of kidney disease.

The American Diabetes Association (ADA) and the National Kidney Foundation (NKF) recommend at least annual screening for CKD by checking a spot urine albumin-to-creatinine ratio (UACR) and eGFR in patients with a diagnosis of type 1 DM of >5-year duration and in all newly diagnosed patients with type 2 DM. Patients with a UACR of >30 mg/g creatinine and or eGFR <60 mL/min/1.73 m^2 should be monitored twice a year to guide therapy [3–5].

For quite some time, it has been recognized that treatments based on inhibition of the renin-angiotensin system (RAS) have significant effects on microalbuminuria, an early marker of vascular dysfunction, and can reduce the rates of cardiovascular morbidity and mortality [6–10].

Recently, inhibition of the sodium-glucose co-transporter 2 (SGLT2) showed combined effects on cardiovascular and renal

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outcomes in DKD patients [11–13]. Other novel treatments, dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP1) agonists, were also demonstrated to improve glycemic control and lower the rates of macroalbuminuria, and also to lower the risk of cardiovascular outcomes, although, to a much lower extent than SGLT2 inhibitors [14, 15].

Another agent, finerenone, which is a nonsteroidal mineralocorticoid antagonist (MRA), has been demonstrated to have long-term efficacy and safety (as compared with placebo) in patients with CKD and type 2 DM [16]. Patients treated with finerenone had an 18% lower risk (as compared with patients treated with placebo) in the rate of the primary kidney endpoint, defined as a composite of time to kidney failure, a sustained decrease of ≥40% in eGFR from baseline over ≥4 weeks or death from renal causes.

Despite advancements in treatment options for slowing CKD progression over the past 30 years, the target annual decline rate still has not been reached [17]. Why is this the case?

Using a cross-sectional study design, Marques *et al.* [18] looked at patients with type 2 DM who were admitted to a university hospital and attempted to look at the prevalence of DKD and the accuracy of the DKD diagnosis. Information was obtained from electronic medical records (EMRs).

Quite intriguingly, CKD and DKD were both demonstrated to be 'significantly underdiagnosed' in this cohort. Less than 10% of patients who fulfilled the diagnostic (laboratory) criteria for DKD were actually labeled as having DKD, whereas only a third of these patients were labeled as having CKD. This finding has important potential implications. Correctly identifying patients with CKD allows the institution of renal protective measures, e.g. avoidance of exposure to potentially nephrotoxic agents, appropriate rendering of measures to slow CKD progression, e.g. blood pressure control, diabetes control, use of statins, correction of metabolic acidosis, etc. Moreover, patients who would have been candidates for appropriate treatment with medications such as SGLT2 inhibitors, GLP1 receptor agonists, DPP-4 inhibitors and nonsteroidal MRAs are likely not receiving optimal treatment.

One has to recognize, however, that there are significant limitations to the study, e.g. cross-sectional design, single center, sample size and use of EMRs.

A prospective study [19] published in 2013, looking at patients with type 2 DM, using a conventional data-based analysis, showed similar DKD prevalence values as demonstrated by the authors in this study, thereby supporting the notion that the study population here is truly representative of the target population.

Affected patients need to know that they have CKD as it is recognized as a 'silent killer' with dire complications that have widespread long-term clinical and economic implications. Based on an analysis of a large US database, less than half of the people who have advanced-stage kidney disease are aware of it [20]. While several publications and guidelines recognize the importance of structured patient-centered educational programs and team-based integrated approaches to DKD, the findings in this study should be an alarm signal that we physicians, as a community, should do better.

Is there a role for novel biomarkers other than UACR and eGFR for early detection of DKD? More studies are needed to determine the utility and practicality of these biomarkers, whether as single or panel. Several genome-wide association studies have identified loci that have been shown to have some association with DKD. However, genetic studies in diverse populations for fine mapping and population-specific associations are still needed.

"The future depends on what you do today."
Mahatma Gandhi

CONFLICT OF INTEREST STATEMENT

Speaker/Advisory Board: Akebia/Otsuka (Vadadustat), Astra Zeneca (Dapagliflozin), Bayer (Finerenone), Glaxo Smith Kline (Daprodustat), Otsuka (Tolvaptan) and Vifor (Difelikefalin). Steering Committee: Bayer (Finerenone).

(See related article by Marques et al. The hidden diabetic kidney disease in a university hospital-based population: a real-world data analysis. *Clin Kidney J* (2022) 15: 1865–1871.)

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