GUEST EDITORIAL

Chronic Kidney Disease with Risk Factor Diabetes: Need for Change in Nomenclature Reflecting Heterogeneity of Kidney Disease in Diabetes

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The International Diabetes Federation estimates that 537 million individuals around the globe currently have diabetes, and this number is anticipated to rise to approximately 783 million by 2045. About 30% or more of individuals diagnosed with diabetes are more prone to developing chronic kidney disease (CKD), and a considerable portion progresses to renal impairment that requires renal replacement therapy.[1,2]

Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes, exceeding 90% of all diagnoses. Even though T2DM is inherently a heterogeneous disease, various clusters have been described with varying risks of developing vascular complications, including nephropathy. In contrast, T1DM is less heterogeneous, with more predictable renal outcomes.[3]

Kidney disease in diabetes was first identified through histological examinations conducted during autopsies of individuals who had diabetes, albuminuria (significant albumin excretion in urine), and renal failure.[4] However, in clinical practice, it is termed diabetic nephropathy and identified as a microvascular complication linked to diabetes.[5]

Classically, diabetic nephropathy is believed to commence with an early rise in glomerular hyperfiltration, which subsequently leads to onset albuminuria. Over time, albuminuria can progress into more severe proteinuria, which may reach the nephrotic range. The estimated glomerular filtration rate (eGFR) typically declines when albuminuria is already present. If no intervention is undertaken, this can lead to advanced stages of CKD. This progression reflects the staging of renal involvement in T1DM as described by Mogensen.[4]

However, recent findings from observational cohort studies, clinical investigations, and mechanistic research examining underlying biological pathways have highlighted the substantial heterogeneity in the presentation and progression of kidney disease in the context of diabetes. These studies reveal distinct patterns in the progression of disease that do not align with the conventional log-linear relationship between urinary albumin excretion, decline in eGFR, and adverse outcomes, particularly in patients with T2DM.[5] Subsequent research has revealed that the classical progression of this pathway in individuals with diabetes and kidney disease is neither linear nor homogeneous and falls short of capturing the full spectrum of biological and clinical heterogeneity.

In the emerging framework, CKD is conceptualized as a complex, multifactorial condition influenced by a wide range of risk factors that extend beyond purely glucocentric considerations. Both modifiable and nonmodifiable factors, such as obesity, hypertension, dyslipidemia, hyperglycemia, smoking, aging, inflammation, low birth weight, low nephron count, oxidative stress, fibrosis, genetic predisposition, previous kidney injury, infectious diseases, environmental exposures, nephrotoxins, and autoimmune conditions, are recognized as contributing risk factors.[4]

Numerous terms, including diabetic nephropathy, diabetic and nondiabetic kidney disease in individuals with diabetes, diabetic and CKD, and nonalbuminuric diabetic kidney disease, are used to describe the complexity and heterogeneity in the diverse manifestations of kidney disease among people with diabetes.[4,5]

For most people with T1DM, diabetes is the main factor leading to kidney disease, and the progression of end-stage kidney disease typically follows a more traditional path after 10–20 years of having diabetes. However, in the case of T2DM, CKD is more multifactorial due to a combination of several CKD risk factors. A retrospective biopsy cohort study found that in 22% of cases, kidney disease was not attributable to diabetes mellitus. Additionally, in 12% of the participants, kidney disease was associated with diabetes and other contributing factors. In this study, 46% of T2DM patients suggested kidney disease was unrelated to diabetes.[6] A systemic review that looked at 40 studies (5,304 data points) of global renal biopsy data between 1977 and 2019 reported that the prevalence of kidney disease due to etiologies unrelated to diabetes, collectively known as nondiabetic kidney disease (NDKD), ranged from 0 to 68.6%, with an average of 40.6%.[7] One of the main criticisms of these retrospective studies is that the observed differences in prevalence may be due to the clinical criteria used by clinicians to perform the renal biopsies. This can introduce a preselection bias, as biopsies are often targeted toward patients with a high clinical suspicion of NDKD.[2]

A prospective cohort study involving untargeted renal biopsies in individuals with T2DM revealed that 35% had a component of NDKD, with NDKD being the sole cause in 18.2% of the cases. This indicates that NDKD is prevalent in T2DM patients with renal involvement. Although multiple studies have indicated that various clinical predictors, such as the duration of diabetes, absence of retinopathy, absence of neuropathy, and presence of hematuria along with RBC casts, can predict NDKD, findings from a prospective study revealed that clinical and laboratory parameters are still inadequate for reliably selecting patients for renal biopsies. Renal biopsy remains the only confirmatory test to distinguish between diabetic kidney disease (DKD) and nondiabetic kidney disease (NDKD) and overlap (both DKD and NDKD).[2] NDKD includes a collection of various kidney disorders that are grouped together under one category, such as IgA nephropathy, membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis (FSGS), and many other causes of kidney disease. NDKD typically leads to a far better prognosis in terms of composite renal outcomes compared to DKD when identified and treated appropriately.[8]

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The Renal Pathology Society's Research Committee has developed a histopathological classification for diabetic kidney disease, creating a consensus system that integrates both type 1 and type 2 diabetic nephropathies (DN). Histopathological classification is based on glomerular, tubular, interstitial inflammation, and vascular involvement, with each parameter having a different grade of involvement. This classification suggests that kidney disease in diabetes is heterogeneous (DKD and NDKD), and even those with DKD are highly heterogeneous, with variable degrees of glomerular, tubular, interstitial, or vascular involvement and different clinical progressions.[9] The follow-up of the prospective biopsy study cohort indicated that combining histopathological features (RPS classes III and IV) with clinical parameters such as proteinuria can help predict worse outcomes in subjects with DKD.[8]

The traditional belief that albuminuria precedes the deterioration of renal function in diabetes has been challenged by the observation of worsening kidney function despite the absence of albuminuria. This condition is referred to as nonalbuminuric kidney disease. Tubulointerstitial pathologies in the kidney have been shown to be associated with renal damage without albuminuria. The prevalence of nonalbuminuric kidney disease is thought to be higher in patients with T2DM than in those with T1DM. Albuminuric DKD is commonly associated with glomerular changes, arteriolar hyalinosis, and interstitial fibrosis, whereas nonalbuminuric DKD more often shows tubular changes and vascular injury. These findings underscore the need for expanding the pathology-based diagnostic framework, which includes alternative mechanisms or pathways of kidney damage and progression in nonalbuminuric types of DKD.[4,5]

Mechanistic studies related to kidney disease in diabetes have revealed that, in addition to hyperglycemia, various other pathological pathways, including epithelial-mesenchymal transition (EMT), fibrosis, which includes transforming growth factor-β–mediated glomerulosclerosis and interstitial fibrosis, chronic inflammation (interleukins and tumor necrosis factor-α), oxidative stress, and tubular injury, are involved, which highlights the heterogeneity in the underlying pathogenesis of the development of the disease.[4,5] More than 80 genetic loci involving both coding and noncoding genes have been identified as contributors to disease onset and progression, resulting in diverse risk profiles.[5]

In 2022, the guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) and the American Diabetes Association–Kidney Disease: Improving Global Outcomes (ADA-KDIGO) introduced the new terminology "diabetes and kidney disease" to describe all kidney-related conditions associated with diabetes, addressing the heterogeneity regarding renal complications in patients living with diabetes.[4] However, nowadays, kidney disease in individuals with diabetes has been reconceptualized as a complex, multifactorial disease, where diabetes is considered a contributing risk factor rather than the sole cause. Reflecting this shift, the KDIGO guidelines have moved away from DKD and coined a new broader term, CKD with risk factor diabetes.[5]

The revised concept of heterogeneity and adoption of the term "CKD with risk factor diabetes" represents not merely a matter of terminology but a pivotal shift toward a better understanding of pathogenesis and management.[5] The primary rationale for addressing disease heterogeneity is to enable disease-specific interventions, including controlling modifiable risk factors through lifestyle modifications. From an intervention perspective, SGLT2 inhibitors (SGLT2i) have been proven to offer renal protection across a range of phenotypes. GLP-1 receptor agonists (GLP-1 RAs) aim to reduce metabolic risk factors and are associated with improved kidney outcomes. In contrast, nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), such as finerenone, provide additional antifibrotic effects and offer potential for precision medicine in patients with diabetes. These medications operate through complementary mechanisms, including regulation of tubuloglomerular feedback, enhancement of natriuresis, and activation of pathways that are anti-inflammatory and antifibrotic, which may result in synergistic benefits when used in combination. Meta-analyses have indicated that the combined use of SGLT2i, GLP-1 RAs, and nsMRAs results in additive renal benefits, underscoring the growing importance of a multimodal therapeutic approach in the management of kidney disease.

To conclude, disease heterogeneity provides deeper insight into the inherent complexity of different subtypes and highlights the need for multi-omics approaches and machine learning algorithms to delineate distinct subtypes to help in diagnosis, prognosis, and determination of specific treatment options.[10]

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