EDITORIAL

Diabetic Kidney Disease – Stumbling blocks, Discoveries and Opportunities in the 21st century

Christopher Thiam Seong Lim

Unit of Nephrology, Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia

Email: christopher@upm.edu.my

Diabetic kidney disease (DKD) is a known complication that develops in around 40% of diabetic patients and it is consistently the leading cause of chronic kidney disease (CKD) universally over the last few decades. Based on the National Health and Morbidity Survey in 2019, approximately 3.9 million Malaysians are living with diabetes. The prevalence has risen from 13.4% in 2015 to 18.3% in 2019. This simply translates to 20 per cent of the adults in the country are living with diabetes, giving Malaysia the infamous nickname of "Sweetest Nation in Asia" (1).

The prevalence of CKD in Malaysia was 9.07% in 2011 and unsurprisingly with DKD as the top contributor (2). A more recent cross-sectional survey in 2018 has revealed that the prevalence of CKD in Malaysia has further increased to 15.48% (3). The increasing prevalence of DKD parallels the global phenomenon of the dramatic rise in the prevalence of diabetes. Hence, the number of prevalent dialysis patients in Malaysia also showed a significant jump from 19,430 in 2008 to 44,136 in 2018 (4).

The classical description of the natural progression of DKD includes glomerular hyperfiltration, development of albuminuria and subsequently proteinuria, declining glomerular filtration rate (GFR) with the corresponding elevated serum creatinine, and ultimately, end-stage kidney disease (ESKD). However, it has now become apparent that some patients with diabetes, regardless of type 1 or 2, do not follow this classical course. For example, of the 28% of the United Kingdom Prospective Diabetes Study (UKPDS) cohort who developed CKD stage 3, half did not have preceding albuminuria (5). Even in the Diabetes Control and Complications Trial (DCCT), of the 11% of patients with type 1 diabetes who developed CKD stage 3, 40% had never experienced macroalbuminuria (6).

While almost all patients with type 1 diabetes eventually develop some degree of retinopathy, only one-third of these patients will develop overt DKD. This suggests that additional risk factors beyond hyperglycaemia must also be involved in the pathogenesis of DKD. Recently, light has been shed on the pathogenesis and emerging risk factors for DKD, which have been broadly classified as susceptibility factors, initiation factors and accelerating factors (7).

Susceptibility factors refer to age, gender, family history and ethnicity. The pattern of family clustering supports the important role of genetic factors in diabetes and CKD/ESKD. A large number of genome-wide association studies (GWAS) have been carried out to identify susceptibility genes in different diabetic cohorts. Some of these recently discovered genes function as pivotal regulators in the pathogenesis of DKD, such as those related to glucose and lipid metabolism. However, the precise functions of most of these genes remain to be elucidated (8).

The strongest initiation factor is attributed to the presence of hyperglycaemia milieu. Hyperglycaemia is associated with the development of overt proteinuria, CKD and ESKD. This is largely supported by two landmark diabetes trials whereby a tight sugar control in the early in the course of disease delays DKD development (9,10). This "legacy effect / metabolic memory," points towards the substantial benefit derived from early intensive glycemic control which is postulated to be mediated through epigenetic alterations.

Once a patient develops DKD, various other factors such as hypertension can act as accelerating factors that hasten the renal deterioration. The impact of hypertension on CKD deterioration is more obvious than the effect of hyperglycaemia on CKD progression. According to the MRFIT study, the adjusted relative risk of reaching ESKD was 1.9 for high-normal blood pressure, 3.1 for stage I, 6.0 for stage II, 11.2 for stage III, and 22.1 for stage IV hypertension (11). Other known accelerators include acute kidney injury (AK), obesity, smoking, high protein diet, interstitial nephritis, over activation of the renin-angiotensin–aldosterone system (RAAS) and toxin induce injury (12). The wide availability and frequency of use of non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors in the last decade, both of which are associated with AKI, may contribute to the rising incidence of AKI within DKD cohorts. Evidence suggests that patients who have recovered from AKI have a 25%

increased risk for developing progressive CKD and ESKD. In addition, these patients demonstrated a 50% increase in mortality after 10 years. Smoking should be discouraged as it can increase the CKD risk through the proinflammatory state, oxidative stress, prothrombotic shift, endothelial dysfunction, glomerulosclerosis and tubular atrophy (13).

The incidence, presentation and course of DKD vary substantially across the continent. For example, patients in the Asia continent have a higher prevalence of elevated urinary albumin/creatinine ratio (ACR) than European populations (14). Annual screening for DKD is advisable for Type 1 DM 5 years after the diagnosis and Type 2 DM as soon as it is diagnosed. The diagnosis of DKD is made based on the measurement of serum creatinine and estimated glomerular filtration rate (GFR), together with quantification of albuminuria along with clinical assessments, such as the duration of diabetes and the presence of diabetic micro and macro-vascular complications. Early referral to a nephrologist (at CKD stage 3) help improve DKD outcomes and should be considered.

On the other hand, the original terminology diabetic nephropathy is only applicable when the patient has classical diabetic changes proven on a renal biopsy. Such changes are heterogeneous and include but are not limited to thickening of the basement membrane, fibrosis, sclerosis, interstitial inflammation, hyalinosis, tubular atrophy and nodular sclerosis (Kimmelstiel–Wilson lesion). Additionally, we also found that the presence of dual pathology in patients with DKD who suffered a rapid kidney function deterioration where our renal biopsy samples showed the presence of Ig A glomerulonephritis, interstitial nephritis, focal segmental global sclerosis and membranous nephropathy (15). Additional renal pathology should be suspected when the patients with DKD has rapidly worsening kidney functions, active urinary sediments, a manifestation of signs or symptoms of other systemic diseases, refractory hypertension, a new-onset nephrotic syndrome and absence of retinopathy. Further study is urgently needed to investigate the influence and mechanism of these ongoing insults that could further hasten the rapid deterioration of kidney function.

Mechanisms that lead to DKD include hyperfiltration damage, advanced glycosylation end products, inflammation, mitochondrial production of reactive oxygen species (ROS) accelerates in response to an increase in intracellular glucose and glomerulotubular dysfunction and fibrosis. Tubulointerstitial fibrosis is widely considered to be the final common pathway for loss of renal function in DKD and has a better correlation with loss of kidney function than glomerular changes. The appearance of fibrogenic cells might be due to the transformation of native renal fibroblasts and mesenchymal stem cells, translocation of fibroblasts from the bone marrow, and adaptive tubule epithelial to mesenchymal differentiation. At the molecular level, numerous cytokines, growth factors and hormones such as transforming growth factor-beta and angiotensin II cause pathologic changes associated with DKD (16).

Despite the latest treatment that involves correction of glycaemia, ACEI inhibitor, angiotensin receptor blocker; DKD patients still experience significant residual risk that put them at risk of joining the perpetual CKD declining slope. To circumvent this dismal clinical picture, urgent efforts in the field of discovery of new DKD biomarkers, a better understanding of the mechanism of DKD and designing clinical trials with standardized and clinical relevant objectives, and development of therapeutic agents targeting kidney-specific disease mechanisms (17).

The newer generation of therapeutic agents has been designed to target the DKD mechanistic pathways, such as glomerular hyperfiltration, inflammation, and fibrosis. Thus far, agents that have shown early success include baricitinib, a selective Janus kinase 1 and Janus kinase 2 inhibitor (18); atrasentan, a selective endothelin A receptor antagonist (19).

More recently, finerenone, a selective nonsteroidal mineralocorticoid receptor that is touted to have anti-fibrotic property, has demonstrated favourable effects on cardiorenal outcomes in patients with predominantly stage 3 or 4 CKD with severely elevated albuminuria and type 2 diabetes without significant risk of hyperkalaemia (20).

Another powerful agent, sodium–glucose cotransporter 2 (SGLT2) inhibitors, apart from decreasing glycated haemoglobin levels, have favourable effects on the kidney and cardiovascular outcomes in large clinical trials involving patients with type 2 diabetes. The SGLT2 is expressed in the proximal tubule and mediates the reabsorption of approximately 90 per cent of the filtered glucose load. SGLT2 inhibitors promote the renal excretion of glucose and they modestly decrease blood sugar, blood pressure and induce weight loss. SGLT2 inhibitors reduce proximal tubular sodium reabsorption, thereby increasing distal sodium delivery to the macula densa, promoting a favourable tubuloglomerular feedback mechanism which is deemed to be renoprotective.

The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial showed that long-term administration of canagliflozin conferred renal and cardiovascular protection in patients with type 2 diabetes with CKD (21). In DAPA-CKD trial, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, ESKD was significantly lower with dapagliflozin than with placebo (22). Among patients with DKD, the risk

of a composite of a sustained decline in the estimated GFR of at least 50%, ESKD, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.

Recent evidence from clinical trials suggests that treatment of type 2 diabetes mellitus (T2DM) with an incretin-based agent such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) confers kidney-protective effects (23). This is evidenced by the data from AWARD trial in which treatment with 1.5 mg duraglutide weekly was associated with a clinically relevant risk reduction of ≥40% eGFR decline or ESKD (24).

The novel concept of combining a glucose-dependent insulinotropic polypeptide with a glucagon-like peptide-1 (GLP-1) receptor agonist takes incretin therapeutic agents to a new level. Tirzepatide is under phase 2 and 3 trials for the treatment of type 2 diabetes. Impressive reductions in body weight and blood pressure, as well as a greater overall improvement in the lipid profile, were observed with tirzepatide while avoiding hypoglycaemia (25). Given the crucial role of obesity in the epidemic of diabetes, the ability of tirzepatide in improving the metabolic profile and sustaining weight loss provide another attractive agent in combating diabetes and DKD.

In summary, a growing and unmet need remain for targeted population-based policy and effective treatment strategies for preventing, arresting and treating DKD. Given the heterogeneous nature of DKD, a personalized treatment approach rather than a one-size-fits-all approach will probably be the way forward in treating this condition in the 21st century.

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