Unit No. 5

EXPERT INSIGHTS FOR PCPS IN MANAGING CKD IN T2DM

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ABSTRACT

Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease (ESRD) in most developed countries including Singapore. Patients with DKD have a disproportionately higher risk for cardiovascular (CV) events and mortality. A comprehensive strategy is recommended for management of patients with DKD to reduce the risks of kidney disease progression and CV disease. Lifestyle modification, CV risk factor and glycaemic control, and maximum tolerated renin-angiotensin-aldosterone-system (RAAS) blockade form the foundation of DKD care. The kidney-protective effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors are well established by randomised controlled trials (RTCs) in patients with DKD, and are independent of the stage of kidney disease. Glucagon-like peptide-1 receptor agonist (GLP-1RA) is the preferred added agent to metformin and SGLT-2 inhibitor if individualised glycaemic targets are not achieved. In addition, the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone improves kidney and cardiovascular outcomes in patients with DKD.

GLOBAL BURDEN OF DIABETES

The global burden of diabetes is enormous, with one in 10 adults currently having diabetes. In 2021, one in 11 adults (90 million) in Southeast Asia were living with diabetes,[1] there were 747,000 deaths caused by diabetes, and global diabetes-related health expenditures were estimated at USD 966 billion.[2]

Approximately 30-40 percent of patients with type 2 diabetes mellitus (T2DM) develop diabetic kidney disease (DKD).[3] DKD is a clinical diagnosis based on albuminuria, low estimated glomerular filtration rate (eGFR), or both in

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diabetes. DKD has been shown to shorten lifespan by 16 years. In Singapore, DKD contributed to 68.2 percent of end-stage kidney disease in 2019.[4] Mortality rates remain high among dialysis patients compared to the general population, and cardiovascular disease (CVD) is the main cause of death.

PATHOPHYSIOLOGY

Diabetic nephropathy (DN) is histologically characterised by glomerular basement thickening, mesangial expansion, nodular glomerular sclerosis, and tubulointerstitial fibrosis.[5] The pathophysiology of DN is a complex interplay between haemodynamic changes, oxidative stress, inflammation, hypoxia, and activation of the renin-angiotensin-aldosterone system (RAAS), leading ultimately to fibrosis in the kidney.

Hyperglycaemia leads to the production of reactive oxygen species and activation of pro-inflammatory pathways, which include protein kinase C, polyol, hexosamine, and advanced glycation end products (AGE). The inflammatory process may damage the endothelium, leading to vasoconstriction and hypoxic injury to the glomerulus. Increased expression of transforming growth factor-beta and vascular permeability result in kidney fibrosis, leading to albuminuria and progressive decline in renal function.[6,7]

Aldosterone is now recognised as a mediator of the progression of renal disease by causing perivascular inflammation,[8] enhanced oxidative stress, direct vasoconstrictive influence on afferent and efferent glomerular arterioles, and fibrosis.

Mineralocorticoid receptors (MRs) are responsible for transcription of multiple genes that provoke inflammation and fibrosis both in the heart and in the kidneys. Mineralocorticoid receptor antagonists (MRAs) reduce renal fibrosis and glomerulosclerosis by deactivating the mineralocorticoid receptor in fibroblasts.[9]

Glomerular hyperfiltration is a well-known consequence of early diabetes.[10] One plausible mechanism of glomerular hyperfiltration is increased proximal tubular reabsorption of glucose via sodium-glucose cotransporter-2 (SGLT-2), which decreases distal delivery of solutes, particularly sodium chloride, to macula densa. The resulting decrease in tubulo-glomerular feedback may dilate the afferent arteriole to increase glomerular perfusion.[11] Concurrently, constriction of efferent arteriole occurs due to high local level of angiotensin II, resulting in changes of autoregulation and glomerular hypertension.[3] The systemic and intra-glomerular hypertension interact with metabolic abnormalities to accelerate renal injury manifested by proteinuria.[12]

RAAS blockade dilates the glomerular efferent arteriole and SGLT-2 inhibition constricts the afferent arteriole. These

synergistic effects lower intra-glomerular pressure, resulting in reduction in proteinuria and long-term stabilisation of renal function.[13]

In humans, glucagon-like peptide-1 receptors (GLP-1Rs) have been identified in the kidney, localised in proximal tubular cells and preglomerular vascular smooth muscle cells.[21] Activation of GLP-1Rs induces natriuresis, diuresis, increased renal blood flow (RPF), and glomerular filtration rate (GFR).[22] In clinical settings, glucose lowering, weight loss, natriuresis, and blood pressure reduction may account for the reno-protective effects of activation of GLP-1Rs.

MANAGEMENT OF DIABETIC PATIENTS WITH CKD

Multifactorial Risk Intervention

Type 2 diabetic patients with CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and CVD. They should maintain a healthy lifestyle and consume a balanced and healthy diet with more vegetables and fruits, and moderation in dietary protein (0.8 g/kg body weight for non-dialysis CKD) and sodium (<2 g/day) intake.[16] Regular moderate intensity exercise, weight loss, and cessation of smoking are recommended (KDIGO).

An individualised HbA1c target ranging from <6.5 percent to <8.0 percent is recommended in patients with diabetes and non-dialysis-dependent CKD.

In the Steno-2 Study, a target-driven, long-term, intensified intervention (target BP <140/85 mm Hg, HbA1c <6.5 percent, Total Cholesterol <190 mg/dL) aimed at multiple risk factors in type 2 diabetic patients with microalbuminuria reduces the risk of cardiovascular and microvascular events by about 50 percent.[17] The relative risk reduction of nephropathy was reduced by 61 percent in the intensive-therapy group compared to the conventional-therapy group.

Multifactorial risk intervention remains the key approach in the management of diabetes worldwide.

RAAS Inhibitors

Optimal control of glycaemia, blood pressure, lipids, and body weight, augmenting the efficacy of RAAS blockade to ameliorate proteinuria, is the current consensus in DKD management.

The reno-protective effect of RAAS blockade in patients with type 2 diabetes and nephropathy was confirmed by both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study and the Irbesartan Diabetic Nephropathy Trial (IDNT).

In the RENAAL study, Losartan resulted in a 16 percent reduction in the risk of composite end point (doubling of

serum creatinine, end-stage renal disease, or death) (P=0.02) in type 2 diabetic patients with nephropathy. The significant improvement in renal outcomes was achieved beyond that attributable to blood pressure control.[18]

In the IDNT, treatment with Irbesartan was associated with a risk of the primary composite end point (doubling of the baseline serum creatinine, onset of end-stage renal disease, or death from any cause) that was 20 percent lower than that in the placebo group (P=0.02) and 23 percent lower than that in the amlodipine group (P=0.006).[19] These effects appeared to be independent of Irbesartan's effects in lowering blood pressure.

Despite the moderately effects of ARBs in RENAAL Study and IDNT, there remains a significant residual risk (40 percent) in preventing CKD progression in patients with type 2 diabetes and CKD.

Recently, novel agents such as SGLT-2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-RAs), and selective non-steroidal mineralocorticoid receptor antagonist (MRA) have been shown in randomised controlled trials (RCTs) to be beneficial in cardiorenal protection.

SGLT-2 Inhibitors

For almost two decades, the therapeutic management of DKD in type 2 diabetes has been centred on blood pressure control, with preferential use of anti-hypertensive agents that attenuate activity of the RAAS.

CREDENCE is the first randomised controlled trial (RCT) to investigate a SGLT-2 inhibitor, primarily canagliflozin for its reno-protective benefit in patients with type 2 diabetes and CKD.[20] In the trial, 4,401 diabetic CKD subjects with albuminuria receiving background standard of care including RAAS blockade were randomised to either canagliflozin 100 mg daily or placebo. The primary endpoint was a composite of doubling of serum creatinine, end-stage kidney disease (ESKD), or death from renal or CV causes. The trial was stopped prematurely over a median follow-up of 2.62 years due to the relative risk reduction of 30 percent in the primary endpoint in those treated with canagliflozin compared to placebo. In addition, canagliflozin treatment was associated with a significant risk reduction in the secondary endpoints of CV death, myocardial infarction, stroke, or hospitalisation for heart failure.

There was no difference in the rates of amputation and fracture between the canagliflozin-treated and the placebo groups. Canagliflozin is currently recommended for the treatment of diabetes with stage 2 and 3 CKD and albuminuria. Those patients who progress to ESKD can continue canagliflozin if already receiving it.

DAPA-CKD trial has confirmed the association of SGLT-2 inhibitors with improved CV and renal outcomes.[21] In the DAPA-CKD, 4,304 participants were randomised to dapagliflozin 10 mg daily or placebo. The primary endpoint

was defined as sustained decline of eGFR of at least 50 percent, ESKD, or death from a renal cause. The trial was stopped prematurely over a median follow-up of 2.4 years due to the hazard ratio (HR) of 0.56 (95 percent CI 0.45-0.68) for a primary endpoint. The HR for a CV outcome was 0.71 (95 percent CI 0.55-0.92). Of note, the CV and renal benefits were similar in those with or without diabetic CKD.

In a recent registry study, prescription of SGLT-2 inhibitors was low in the CKD population, particularly among patients without diabetes.[22]

The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends initiating an SGLT-2 inhibitor in patients who have CKD with an eGFR of 30 mL/min/1.73 m² or higher and albuminuria with or without diabetes. An SGLT-2 inhibitor may be continued for kidney production if the eGFR falls below 30 mL/min/1.73 m².

GLP-1 Receptor Agonists

RCTs of GLP-1 receptor agonists investigated primarily CV outcomes. Both (GLP-1RAs) liraglutide (LEADER trial)[23] and semaglutide (SUSTAIN-6 trial)[24] have shown significant CV risk reduction in patients with type 2 diabetes and high risk for CV complications. Both trials included secondary renal endpoint defined as onset of proteinuria, doubling of serum creatinine, and the need for renal replacement therapy. Both trials showed reduction in renal endpoint, mainly driven by lower rates of macroalbuminuria.

In the SUSTAIN-6 trial, semaglutide significantly lowered the composite renal outcome of new or worsening nephropathy (HR 0.64 95 percent CI: 0.46;0.88, P=0.005) compared to placebo. This was driven largely by reduction in risk of persistent macroalbuminuria (HR 0.54 CI:0.37;0.77, P=0.001). Over the course of the trial, the changes in eGFR from baseline were generally similar between semaglutide and placebo.

The American Diabetes Association (ADA) recommends GLP-As and SGLT-2 inhibitors for cardiac and renal protection in high-risk patients with type 2 diabetes regardless of HbA1c level.[25]

GLP-As are recommended as first-line injection therapy over insulin for type 2 diabetic patients. In addition to metformin according to the level of renal function and SGLT-2 inhibitor, GLP-1 RA is the preferred add-on agent to achieve glycaemic target in T2DM patients with CKD. However, the choice of anti-glycaemic agents after metformin and SGLT-2 inhibitor is influenced by factors such as underlying CVD, risk of hypoglycaemia, levels of renal function, and cost.[16]

Non-Steroidal Mineralocorticoid Receptor Antagonist

Finerenone is a novel selective, non-steroidal mineralocorticoid receptor antagonist (MRA) that blocks the MR. In preclinical models, finerenone inhibits inflammation and fibrosis, thereby protecting against adverse renal and cardiovascular outcomes.[26,27]

In FIDELIO-DKD, finerenone was tested in adults with T2DM and CKD.[28] Inclusion criteria included GFR 25-75 ml/min/1.73m², albuminuria 300-5,000 mg/g, and potassium <4.8 mmol/L. 13,911 subjects randomised to finerenone 10 or 20 mg or placebo and followed up for 2.6 years.

Finerenone significantly retarded CKD progression by 18 percent vs placebo in patients with advanced CKD in T2DM, irrespective of baseline use of SGLT2-inhibitor and GLP-1RAs. Finerenone also resulted in significantly lower risk of CV events than placebo. The incidence of hyperkalaemia-related discontinuation of the trial regimen was higher with finerenone than with placebo.

CONCLUSION

Patients with T2DM and CKD are at high risk for CV events and renal disease progression. Lifestyle modification, CV risk reduction, optimisation of glycaemic control, maximum RAAS blockade, SGLT-2 inhibition, GLP-1R agonism, and MRA receptor antagonism with finerenone provide incremental opportunity to reduce cardio-renal risk in patients with T2DM and CKD.

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LEARNING POINTS

- **Diabetic kidney disease is the most common cause of end-stage kidney disease.**

- **A comprehensive strategy in the management of diabetic kidney disease is recommended.**

- **Novel anti-diabetic agents, SGLT-2 inhibitors, GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonist provide incremental opportunity in reducing the risks of kidney disease progression and cardiovascular disease.**