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Diabetic kidney disease: Its current trends and future therapeutic perspectives

Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease worldwide, and is induced by hyperglycemia, obesity and high blood pressure[1]. Despite good control of blood glucose, blood pressure and lipid levels[2], the remaining risk for end-stage renal disease is still high, showing an urgent need for new therapeutic strategies to prevent the development and progression of DKD. The present and others have identified the underlying mechanism by which diabetes and hyperglycemia induce DKD, such as protein kinase C activation, increased levels of cytokines, advanced glycation end-products, oxidative stress and altered stress responses[3–8]. However, all drugs have failed to prevent the development and progression of DKD in human trials. Based on previous evidence, such as that from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT)[1], renin–angiotensin–aldosterone inhibitors have been recognized as a specific drug for DKD. Renin–angiotensin–aldosterone inhibitors definitely reduce albuminuria, but fail to inhibit renal function decline, resulting in a decreased prevalence of albuminuric DKD and an increased prevalence of estimated glomerular filtration rate (eGFR) decline DKD[9,10].

In the past 4 years, sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to have a high ability to intervene in the progression of DKD in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG Outcome) study, Canagliflozin Cardiovascular Assessment Study (CANVAS) program and Dapagliflozin Effect on Cardiovascular Events (DECLAIR TIMI 58) study [11]. In patients with a past history of cardiovascular events, SGLT2 inhibitors reduced the renal end-points by 44%. In patients without a past history of cardiovascular events, SGLT2 inhibitors reduced the renal endpoints by 46%. Furthermore, Kadowaki *et al.*[12] provided the first evidence in Asia that empagliflozin reduces the risk of the development or progression of DKD by 36%, the risk of progression to macroalbuminuria by 36%, and the composite risk of the doubling of serum creatinine and the initiation of renal-replacement therapy or renal death by 52%. However, the renal end-points have not been set as the primary outcomes, but rather as the secondary outcomes, and therefore, these drugs are not recommended for DKD. Interestingly, Miyoshi *et al.*[13] reported that even in type 2 diabetes patients with eGFR <60 mL/min/1.73 m^2, 2-year treatment with SGLT2 inhibitors significantly preserved the eGFR compared with treatment with non-SGLT2 inhibitors. Surprisingly, in the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study, the primary outcome was a composite of end-stage renal disease, the doubling of the serum creatinine level and death from renal or cardiovascular disease. The canagliflozin treatment group reduced the primary outcome by 30% compared with the placebo group[14].

It is important to know the underlying mechanisms by which SGLT2 inhibitors exert DKD protection. SGLT2 inhibitors reduce high levels of glucose, systolic blood pressure, bodyweight, uric acid and ectopic fat, whereas they increase the levels of hematocrit and high-density lipoprotein cholesterol. Thus, SGLT2 inhibitors have systematic pleiotropic effects, thereby protecting the kidney from diabetic conditions. One of the other mechanisms is the normalization of altered tubuloglomerular feedback induced by diabetic conditions (Figure 1). This results in the normalization of diabetes-induced glomerular hyperfiltration and higher intraglomerular pressure, which are well-known accelerators of kidney injury. Recently, emerging evidence has focused on diabetes-induced tubulointerstitial fibrosis, which is the end-stage of kidney injury, resulting in the loss of renal function[7]. We also hypothesized that the direct toxicity of diabetes-induced reabsorbed glucose and Na^+ overload in the proximal tubular cells as a result of SGLT2 could result in tubulointerstitial fibrosis and nephron loss. We fed C57BL/6 mice a high-fat diet for 8 weeks, and divided them into groups receiving the vehicle or ipragliflozin treatment for another 8 weeks[15]. Although mice with ipragliflozin treatment gained more weight and had higher glucose levels, the renal histology showed that high-fat diet-fed mice displayed tubular vacuolation, dilatation and epithelial cell detachment, which were not observed in control mice; the administration of ipragliflozin ameliorated these alterations. In ultrastructural analysis, the tubular mitochondria of high-fat diet-fed mice showed significant damage, such as ballooning and the loss of cristae, and ipragliflozin treatment reversed the damage, restoring optic atrophy factor 1 and

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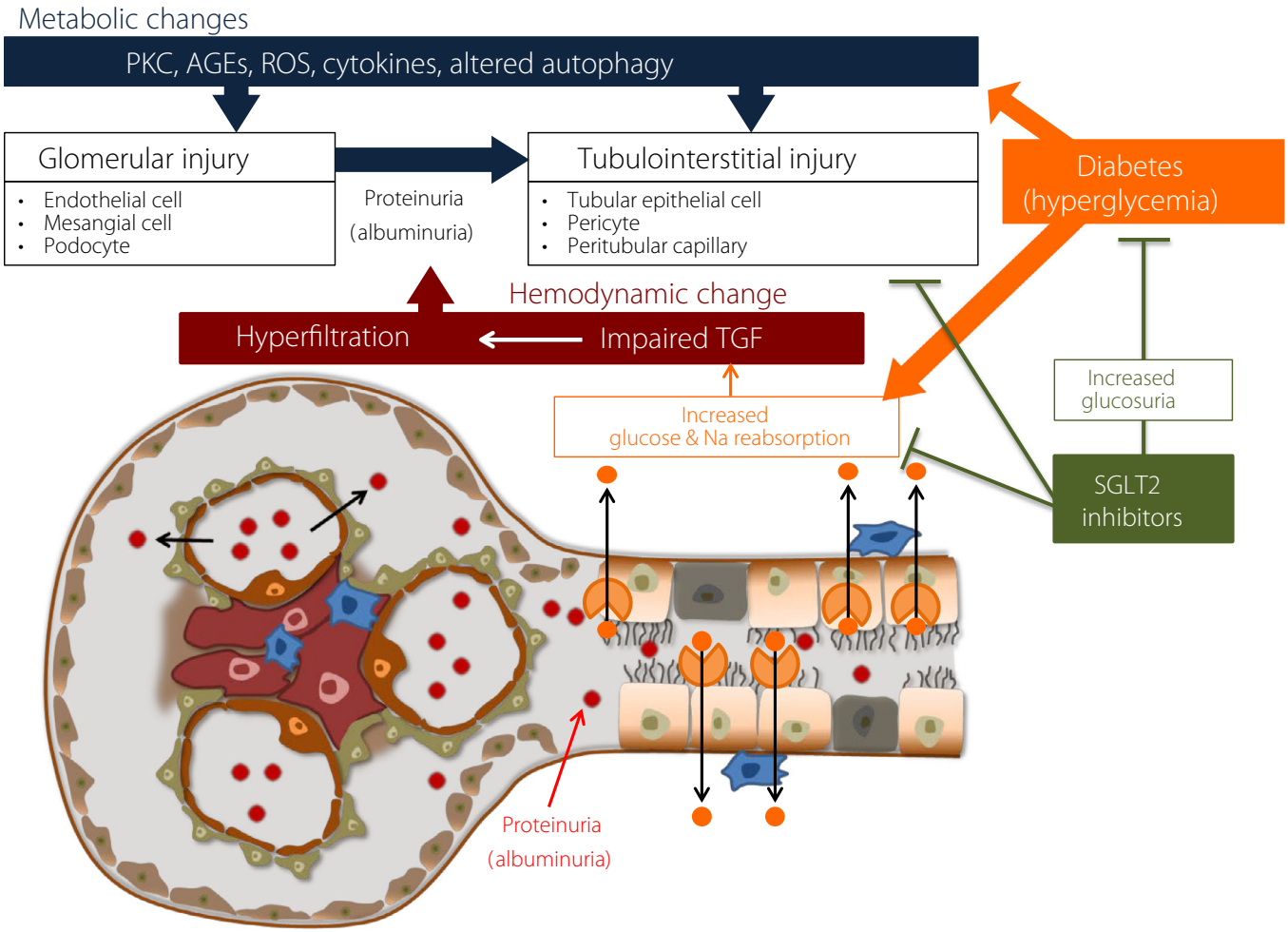

Figure 1 | Renoprotective effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors. Diabetes-induced hyperglycemia, high blood pressure, high uric acid levels and dyslipidemia causes protein kinase C (PKC) activation, oxidative stress, increased levels of cytokines, and altered autophagy in glomerular cells and proximal tubular epithelial cells, in addition to hemodynamic disarrangement (altered tubuloglomerular feedback; TGF), resulting in glomerular and tubulointerstitial injury. After diabetic kidney disease develops, it can progress to end-stage renal disease, requiring renal-replacement therapy or renal transplantation. Recent evidence has shown that SGLT2 inhibitors not only systemically improve metabolic abnormalities, but also reverse altered tubuloglomerular feedback (TGF) and direct proximal tubulointerstitial injury. AGEs, advanced glycation end-products; ROS, reactive oxygen species.

mitofusion 2 levels. SGLT2 inhibition could act directly on tubular cells and protect kidney tubular cells from mitochondrial damage as a result of metabolic insults regardless of blood glucose levels or the improvement in bodyweight reduction (Figure 1). SGLT2 inhibitors could contribute to the fight against DKD development and progression in future.

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DISCLOSURE

The author declares no conflict of interest.

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