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REVIEW

Emerging roles of Sodium-glucose cotransporter 2 inhibitors in Diabetic kidney disease

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Abstract

Diabetic kidney disease (DKD), a severe microvascular complication of diabetes mellitus, is the primary cause of end stage renal disease (ESRD). Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of novel anti-diabetic drugs for DKD, which have the potential to prevent renal function from failing. The involved mechanisms have garnered considerable attention. Besides hypoglycemic effect, it seems that various glucose-independent nephroprotective mechanisms also have a role. Among them, improvement in tubuloglomerular feedback is considered as the main reason, followed by reduced intraglomerular pressure and fluid load. In addition, reduced blood pressure, anti-inflammatory effects, nutrient deprivation signaling as well as improved endothelial function are also important. In the future, clinical trials and mechanistic studies might further complement the current knowledge on SGLT2 inhibitors and facilitate to translate these agents to clinical use. Here, we review these mechanisms of SGLT2 inhibitors with an emphasis on kidney protective effects.

Keywords Sodium-glucose cotransporter 2 inhibitors · Diabetic kidney disease · Diabetes mellitus

Introduction

Diabetic kidney disease (DKD), one of the most common microvascular complications of diabetes mellitus, is projected to affect almost 700 million adults by 2045.[1] As the leading cause of end stage renal disease (ESRD) around the world, DKD can lead to a reduced life expectancy and tremendous economic burdens. This chronic progressive disorder is also the main reason for dialysis or kidney transplant currently.[2] In addition to the mainstay of current therapies consisting of restrict blood glucose control and blood pressure control with renin-angiotensin system (RAS) blockade, however, there is lack of long-term effective treatment for DKD.[3].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a novel class of anti-diabetic agents, have ushered in optimism and hope for the treatment of DKD.[4] These drugs exert significant glucose-lowering effects by blunting glucose reabsorption from the glomerular filtrate through blocking SGLT2 transporter. Results from completed large clinical trials of SGLT2 inhibitors have demonstrated their surprising potential to slow the development and progression of kidney diseases in people with type 2 diabetes mellitus (T2DM) consistently. Recent large cardiovascular outcome trials with SGLT2 inhibitors, such as EMPA-REG OUTCOME with empagliflozin, the CANVAS Program with canagliflozin and DECLARE TIMI-58 with dapagliflozin, all showed unexpected amelioration in renal outcomes which were determined as secondary end points at the beginning of these trials.[5–7] CREDENCE with canagliflozin was a large prospective study specifically designed to explore the efficacy of canagliflozin in patients with established DKD. During this trial, canagliflozin significantly reduced relative risk of primary composite renal outcome comprising ESRD, a doubling of the serum creatinine level, or death from renal or cardiovascular causes.[8] According to the positive results from these trials linked to canagliflozin, the United States Food and Drug Administration (FDA) has approved this agent to apply to patients with diabetes and chronic kidney disease in 2019.[9].

Of note, renoprotection of SGLT2 inhibitors observed in these studies seems not only dependent on glucose-lowering effects. Many non-glycaemic pathways are likely to

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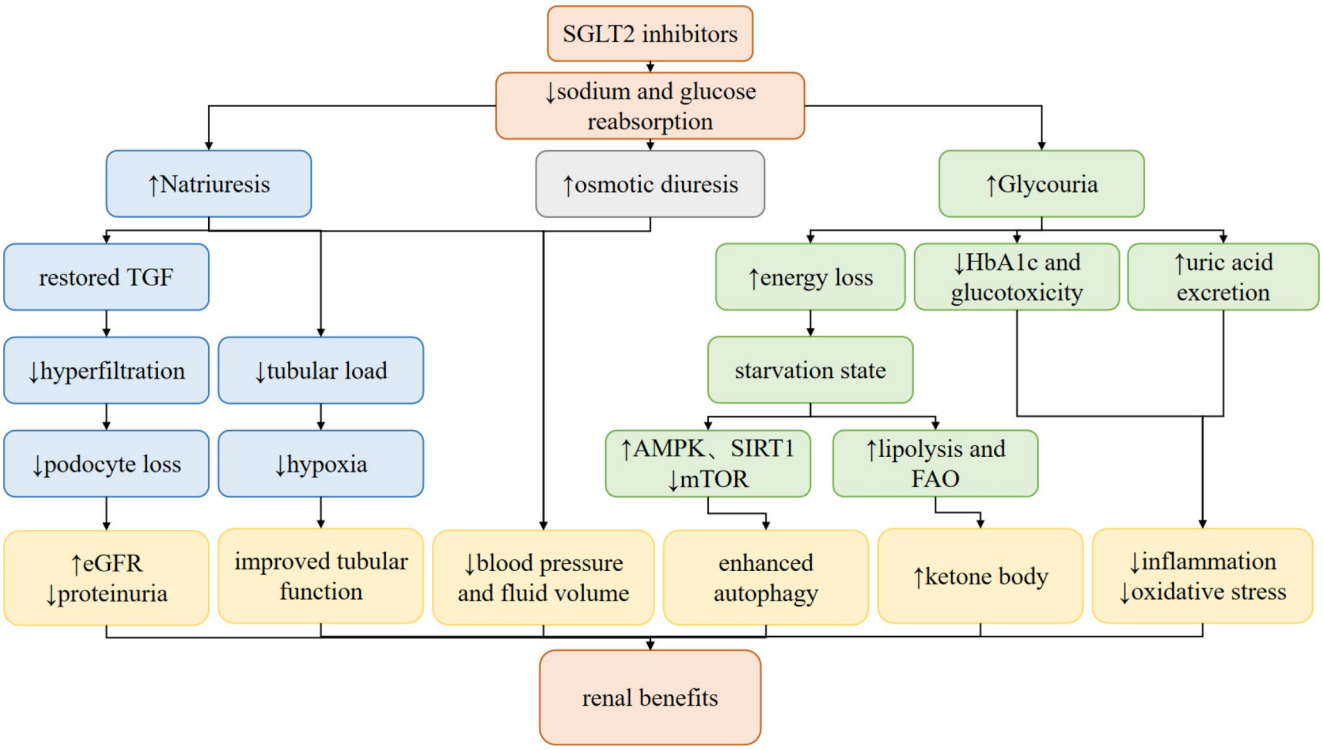

Fig. 1 Renal protective mechanisms of SGLT2 inhibitors

be involved in improved renal function with SGLT2 inhibition. As a result, emerging well-designed clinical trials and mechanistic experiments are designed to provide new insight into protective effects of these drugs. On the basis of these studies recently, we summarize available evidence and discuss potential mechanisms underlying the renal protection of SGLT2 inhibitors. In the following review, we will first describe SGLT2 and its inhibitors in brief. Next, we focus on major and secondary mechanisms of SGLT2 inhibitors in renal protection, with an emphasis on effects independent of glycaemic control. (Fig. 1)

SGLT2 and SGLT2 inhibitors

SGLTs belong to a family of membrane proteins and have the potential to transport glucose, some ions as well as amino acids. The main members of SGLT family are consist of SGLT1 and SGLT2. SGLT1 is primarily found in intestinal tract, while SGLT2 is mainly located in the early S1/S2 proximal tubule segment and responsible for approximately 80 – 90% glucose reabsorption from the glomerular filtrate. The remaining glucose is reabsorbed by SGLT1 in the late S2/S3 tubule segment.[10, 11] Ascribed to active glucose cotransport, almost all of glucose in the filtrate is reabsorbed under normoglycemic conditions. Due to the key role of SGLT2 in tubular reabsorption, inhibiting this transporter is thought to be a promising therapy in patients with T2DM. The first discovered SGLT2 inhibitor, phlorizin, extracted from the root bark of the apple tree, has non-selective inhibitory effects on SGLT2 and SGLT1. It was surprisingly found to have the potential to normalize the level of blood glucose and restore insulin sensitivity in diabetic rats without an intact pancreas in the twentieth century.[12] Owing to low oral bioavailability and adverse effects of phlorizin, it was unsuitable for clinical application. Subsequently, contemporary anti-diabetic drugs with higher selectivity for SGLT2 over SGLT1 and rapid oral absorption were developed. Four kinds of SGLT2 inhibitors are currently approved by FDA, including empagliflozin, canagliflozin, dapagliflozin, ertugliflozin. (Fig. 2)

Renoprotective effects with SGLT2 inhibitiors

Glycaemic control

Hyperglycaemia is considered as an important initial factor in DKD. Under diabetic condition, SGLT2 expression is upregulated in response to increased glucose in tubule. As a result, excessive glucose is reabsorbed from the filtrate to circulation, contributing to sustaining high plasma glucose concentrations. A great number of studies in real-world

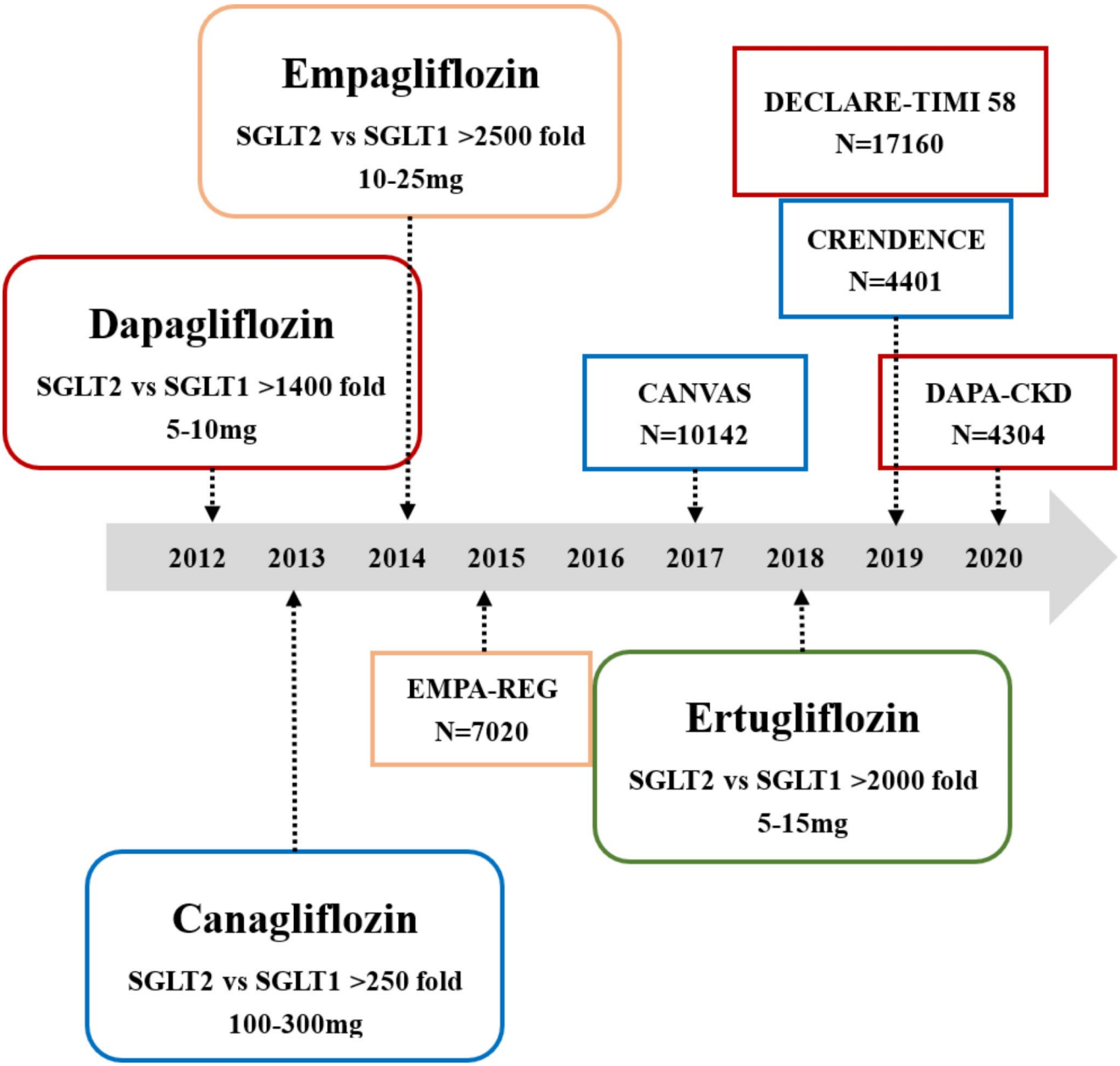

Fig. 2 History, selectivity and dose of dapagliflozin, canagliflozin, empagliflozin and ertugliflozin

settings demonstrate that SGLT2 inhibitors reduce the level of fasting blood glucose and improve oral glucose tolerance in patients with T2DM, along with a slight amelioration in glycated hemoglobin (HbA1c) level.[13] Through blocking active reabsorption of SGLT2 and increasing urinary glucose excretion, these agents exert substantial glucose-lowering activity. Interestingly, this property is independent on insulin secretion. In addition, due to compensatory mechanism in kidney, when pharmacological inhibitor of SGLT2 is applied, SGLT1-mediated transport will be upregulated to reabsorb 40-50% glucose from the tubule. Hence, hypoglycemia is less likely to be observed with SGLT2 inhibitors than other traditional anti-diabetic agents. SGLT2 inhibitors play a significant role in maintaining glucose homoeostasis. Results from a study in mice with T2DM demonstrate dapagliflozin enhances renal gluconeogenesis and increase levels of enzyme associated with gluconeogenesis.[14] This finding is consistent with several randomized controlled researches in real-world settings. Increased endogenous glucose production is observed with SGLT2 inhibitor therapy, even in patients with T2DM after renal denervation or oral glucose load.[15, 16] Of note, the improved glycaemic control is unlikely fully to explain the renal benefits with

SGLT2 inhibitors, suggesting additional renal mechanisms also work.

In addition to SGLT2 inhibition, there are many emerging anti-diabetic drugs, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase IV inhibitors (DPP4i). Many studies are designed to evaluate the benefits and safety of these agents combined with SGLT2 inhibitors. Data from a meta-analysis demonstrates a greater reduction in HbA1c and fasting plasma glucose is induced by combination therapy with SGLT2 inhibition and GLP-1 RAs than monotherapy.[17] This similar glucose-lowering effects are also observed in a rat model of T2DM with dual inhibition of DPP4 and SGLT2.[18] Of note, the risk of hypoglycaemia is significantly with combination therapy.

Natriuresis and reduction in blood pressure

Hypertension is of great significance in accelerating the progression of DKD. A meta-analysis based on clinical studies suggests that SGLT2 inhibitors are able to decrease both systolic and diastolic blood pressure.[19] Currently, natriuresis and osmotic diuresis are thought to be the main reason for the blood pressure-lowering effect with SGLT2 inhibitors. Due to the coupled reabsorption of glucose and sodium, inhibition of SGLT2 in the proximal tubule contributes to enhanced sodium excretion and reduced plasma volume following by decreased blood pressure. In addition, RAAS blockade with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is a class of traditional drugs for hypertension control in DKD. Recently, several studies are devoted to evaluate the efficiency of combination therapy with SGLT2 inhibitors and RAAS blockade in the setting of diabetes. In an animal model of DKD with established hypertension, combination treatment with lisinopril and empagliflozin demonstrates synergistic effect on renal protection with comparison to ACEI/ARBs alone.[20] The finding is further supported by evidence in real-world condition. A meta-analysis based on clinical researches suggests that the combination therapy could achieve a better control of hypertension and hyperglycaemia than monotherapy, leading to improved renal outcomes. Moreover, it should be noted that the risk of hypoglycaemia is also increased.[21].

Interestingly, aside from SGLT2, a growing body of studies have demonstrated additional ion transporters are also implicated in sodium transport and water-salt balance in the tubule. NaCl cotransporter, located in the distal convoluted tubule, is one of the important transporters responsible for blood pressure control. In a model of obesity and diabetes, SGLT2 inhibitors enhance natriuresis and reduce renal reabsorption via regulating activity of this cotransporter indirectly.[22] What's more, another ion transporter, sodium-hydrogen exchanger 3 (NHE3), which functions to mediate almost 70% of sodium reabsorption in the proximal tubule, is found to be upregulated in the context of diabetes. The upregulation of NHE3 expression is complicated in maintaining high level of blood pressure. Interestingly, NHE3 is colocalized with SGLT2 in the kidney and their activity is tightly linked to each other.[23] Inhibition of SGLT2 has been proved to effectively modulating NHE3 activity negatively, while natriuresis induced by SGLT2 inhibitors is reduced in tubule-specific NHE3 knock-down mice. The phenomenon suggests that part of natriuresis by SGLT2 inhibitors is mediated by suppressing NHE3, resulting in improved renal salt and water handling, reduced fluid load and relieved hypertension.[24–26] Of note, in the setting of non-diabetic heart failure, empagliflozin also exerts inhibitory effect on NHE3, suggesting that suppression on NHE3 by this agent is present in both absence and presence of diabetes, while the detailed mechanism remains to be elucidated. Furthermore, another sodium-hydrogen exchanger NHE1 which is ubiquitously expressed in the heart, provides a novel insight into off-target effects by SGLT2 inhibitors in cardiomyocytes.[27] Whether the downregulation of NHE3 in response to SGLT2 inhibitors in kidney could exert similar influence which is analogous to NHE1 in cardiomyocytes has not been determined.

Restored tubuloglomerular feedback

Hyperfiltration in glomeruli is one of the key characters of DKD. In the setting of diabetes, renal proximal tubule will become maladaptive hypertrophy and SGLT2 expression is also excessively upregulated in response to heavy glucose load in tubule. Hence, upstream glucose and sodium reabsorption is increased through active transporters, resulting in reduced sodium delivery to the macula densa of the juxtaglomerular apparatus. As a consequence, decreased sodium concentration is sensed by the macula densa, which contributes to the activation of tubuloglomerular feedback (TGF) and changes in diameters of afferent and efferent arteriolar. Excessive TGF activation plays a central role in sustained hyperfiltration and high intraglomerular pressure, leading to serious glomerular basement membrane (GBM) damage and podocyte loss.[28] It is generally recognized that restoration in TGF is the primary mechanism responsible for the glucose-independent benefits of SGLT2 inhibitors in kidney. In many large clinical trials, a slight estimated glomerular filtration rate (eGFR) dip after initial treatment with SGLT2 inhibitors is observed, suggesting direct hemodynamic effects of these drugs.[29] SGLT2 inhibitors will blunt upstream sodium and glucose reabsorption, hence increase sodium delivery to macula densa. As a result, this

signal received by macula densa leads to a reduction in intraglomerular pressure and hyperfiltration via restored TGF. Of interest, Adenosine signaling is proved to play an important role in this process, although there are some differences in different models of diabetes. In a murine model of type 1 diabetes (T1DM), empagliflozin activates A1 adenosine receptor which resulted in afferent arteriolar vasoconstriction, while efferent vasodilation via A2 adenosine receptor is observed in response to dapagliflozin among T2DM population.[30] Altered adenosine signaling seems to work in a context-dependent manner. There may be an explanation for this difference that increased vasoactive prostaglandin will counteract the vasoconstrictive effect of A1 adenosine activation in the setting of T2DM.[31] In addition, functional and structural variances in DKD between T1DM and T2DM are equally important. The restoration of TGF and decrease of intraglomerular pressure with SGLT2 inhibitors protect podocyte integrity and function and reduce excretion of proteinuria.[32] Clinical evidence in patients with SGLT2 inhibition supports this notion that these agents exert structural benefits on glomerular health.[33] Furthermore, hyperreabsorption and activated TGF also contribute to heavy energy consumption and hypoxia in kidney. Renal hemodynamic effects with SGLT2 inhibition mitigate tubular workload and improve renal cortical oxygenation, thus protecting tubular epithelial cells from injuries.

Reduced inflammation

Chronic inflammation is a significant factor accounting for initiation and progression of renal dysfunction. Macrophages are considered as the primary immune cells mediating inflammatory process, which are mainly consist of two subsets: pro-inflammatory M1 subset and anti-inflammatory M2 subset. They will differentiate into M1 phenotype and be recruited into injured kidney under hyperglycaemic condition. There is mounting evidence indicating that SGLT2 inhibitors function to decrease the cellular inflammation responses through limiting activation of macrophages and releases of inflammatory markers. Data from a randomized controlled trial in people with T2DM shows empagliflozin switches circulating monocytes to M2 phenotype and leads to a decline in systemic inflammatory granulocyte burden.[34] A downregulation in inflammatory and fibrotic biomarkers, including TNF receptor 1 (TNFR1), IL-6, matrix metalloproteinase 7 (MMP7) and fibronectin 1 (FN1), is also observed in a study with a clinically relevant concentration of canagliflozin, while another anti-diabetic drug glimepiride fails to reduce these molecules.[35] This finding is consistent with a recent human clinical trial with empagliflozin. Compared to sulfonylurea, this agent induces a greater reduction in pyrin domain-containing 3 (NLRP3) inflammasome and IL-1β secretion in macrophages, secondary to decreased levels of serum insulin, glucose, as well as increased serum β-hydroxybutyrate (BHB).[36, 37] With the development of co-culture technology, more and more studies are designed to explore the communication between parenchymal kidney cells and circulating pro-inflammatory cells. A recent study reveals that injured tubular epithelial cells (TECs) could communicate with inflammatory cells and facilitate macrophages polarization through releasing exosomes, leading to exacerbated renal injuries.[38] Nevertheless, improved TECs function with SGLT2 inhibitors may prevent this vicious circle, providing a new insight into reduced level of inflammation induced by these drugs. kidney is widely known as a heterogeneous organ containing various cells. Further researches are needed to elucidate the sophisticated crosstalk among other cell types including mesangial cells, endothelial cells and podocytes during DKD.

Besides these molecules above, high level of plasma uric acid is also related to inflammatory process in DKD progression. Recently, in an analysis of randomized clinical trials, enhanced uric acid excretion and reduced circulating uric acid are observed with dapagliflozin, which are strongly associated with increased urinary glucose excretion.[39] Restored uric acid level is proved to contribute to mitigated inflammation.[40] In addition, SGLT2 inhibitors have been reported to decrease kidney injury molecule-1 (KIM-1) previously, one of proximal biomarkers in diseases regarding kidney injury.[41] Lately, an interesting study in mice with KIM-1 mucin domain mutant shows that KIM-1 contributes to tubulointerstitial inflammation by mediating proximal tubule cells uptake of fatty acid (FA)-bound albumin.[42] Further study is required to illustrate whether renal anti-inflammatory benefits with SGLT2 inhibitors are associated with suppression of KIM-1.

Nutrient deprivation signaling

Besides the mechanisms described above, emerging studies offer further insights into metabolic alterations and energy homeostasis after SGLT2 inhibitors treatment. Aberrant glycolysis and impaired fatty acid oxidation (FAO) followed by remarkable lipid accumulation in kidney are observed in people and mice in the context of diabetes, a state of energy overabundance.[43] Excitingly, dapagliflozin and ipragliflozin have the potential to suppress this abnormal metabolic state, through increasing the level of key enzyme carnitine palmitoyl-transferase-1α (CPT1α) associated with FAO and decreasing accumulation of tricarboxylic acid (TCA) cycle metabolites.[44] In addition, people and animals with SGLT2 inhibitors manifest a consistent reduction in body weight, which is thought to result from enhanced

urinary glucose excretion and calorie loss. Hence, there is a novel hypothesis that these agents have the potential to switch perceived nutrient overabundance to an energy-preserving state, reminiscent of a state occurring in hibernating animals.[45] In a randomized, double-blind trial, five weeks treatment with dapagliflozin results in improved systemic energy metabolism and increased lipolysis and ketogenesis.[46] The improvement in extracellular lipidome secondary to restored FAO is also observed in db/db mice and Zucker diabetic fatty rats through non-targeted and targeted metabolome technologies.[47, 48] Studies in diabetic mouse models have further shown SGLT2 inhibitors contribute to increased circulating ketone bodies by modulation of rate-limiting enzyme for ketogenesis in various organs.[49] Ketogenesis in the context of SGLT2 inhibitors is thought to be a result of activation of low-energy sensors including 5′ AMP–activated protein kinase (AMPK) and sirtuin-1 (SIRT1), along with the upregulation of hypoxia-inducible factor (HIF)-2α. Ketone is used to be considered as a preferred energy source for injured proximal tubular epithelial cells (PTECs), leading to efficient energy utilization in kidney.[50] Of interest, it is also observed to act as a signal mediator of fasting and induce inhibition of mechanistic target of rapamycin (mTOR) recently. Inhibition of mTOR complex1 has been found to have effects on reducing renal fibrogenesis, mediating the beneficial effects of SGLT2 inhibitors.[51–53] In addition to elevated ketone bodies, reduced branched-chain amino acids transport is also responsible for fasting-like transcriptional paradigm. Changes in key nutrient-sensing pathways facilitate adaption to a low-energy state, with inhibition of energy storage and promotion of energy utilization, ultimately protect the kidney.[54] It should be mentioned that most findings presented herein are based on studies performed in animal models. Well-designed studies will be required urgently to determine the hypothesis and gather further evidence from human studies.

Interestingly, coordinated activation of SIRT1 and AMPK, as well as downregulation of mTOR stimulate autophagy in the setting of SGLT2 inhibitors, leading to clearance of dysfunctional mitochondria and peroxisomes. This reduces major sources of reactive oxygen species (ROS), thus mitigating oxidative stress in kidney.[55, 56] Of note, hyperactive autophagy as well as insufficient autophagy are both considered to be harmful. Reduction of autophagy activity by SGLT2 inhibitors was found recently to protect myocardial cell from death during ischemia-reperfusion injury. It is in contradiction with previous studies in kidney. The exact mechanism by which SGLT2 inhibition optimizes autophagy process in different contexts remains to be illuminated.

Improved endothelial function

Vascular stiffness, endothelial dysfunction and secondary glomerulosclerosis under hyperglycemic condition, as we all know, are critically linked to pathogenesis of DKD.[57] Reduced inflammation and mitochondria dysfunction mentioned above by SGLT2 inhibitors have been proved to involve in the mitigation of endothelial dysfunction. In a mechanistic study, inhibition with SGLT2 ameliorates renal endothelial rarefaction which often contributes to secondary glomerulosclerosis, through restoring level of vascular endothelial growth factor (VEGF)-A.[58] In addition, oxidative stress in the context of diabetes plays an important role in endothelial injuries. A recent study in human cardiac myocytes provides a novel translational link between the dual SGLT2 inhibitor canagliflozin and oxidative stress regulation. Canagliflozin exerts remarkable anti-oxidative effects through a SGLT1 dependent mechanism, resulting in inhibition of NADPH oxidase activity and improvement of nitric oxide synthases function.[59] Interestingly, reduced ROS production with empagliflozin is also observed in human endothelial cells, which is attributed to inhibition on NHE1.[60] Of note, increased the level of circulating pro-vascular cells in the context of SGLT2 inhibitors is also thought to be related to improved endothelial repair.[34] Dapagliflozin is observed to have the potential to improve vascular endothelial healing in diabetic mice, at least in part by recruitment of bone marrow derived hematopoietic cells.[61] Recently, data from human and rodent cells shows canagliflozin inhibits excessive replication and migration of vascular smooth muscle cells (SMCs), as well as mitigates endothelial inflammation, resulting in blunting atherosclerosis and glomerulosclerosis.[62] Regretfully, the exact molecule mechanisms have not been determined. Going forward, it will be important to examine further the dedicated mechanisms of SGLT2 inhibitors on vascular endothelial benefits.

Apart from mechanisms mentioned, suppression of AGE-RAGE signaling, increased hematocrit, provide additional support to improved kidney outcomes by these drugs.[63–65] Taken together, SGLT2 inhibitors should be considered as a predominant clinical therapy after metformin in most people with DKD as a consequence of organ protective effects.

Conclusions

Traditional studies in the past have shown that glomerular lesions play a pivotal role in development of DKD, while recent findings indicate tubular damage may precede lesions in podocytes in early DKD. This observation makes the

tubular hypothesis popular.[66] As a class of drugs directly targeting tubular function in kidney, SGLT2 inhibitors receive great notice. Furthermore, consistent beneficial renal results from recent clinical trials contribute to considerable attention to clinical application of SGLT2 inhibitors in people with diabetes and chronic kidney disease.[67] Emerging studies are designed to explore reno-protective effects with SGLT2 inhibition in people with T1DM, and even without diabetes. Currently, another large clinical study, the EMPA-KIDNEY trial, will provide extra evidence about renal benefits of SGLT2 inhibitors in the context of T1DM.[68] Of interest, many extrarenal effects with these agents also come into notice. In a randomized controlled trial, empagliflozin is associated with improved hypothalamus functions and cognition which indicates a promising approach to treat diabetes-related brain diseases.[69] Significant changes in gut microbiota are also observed with dapagliflozin, suggesting pleiotropic effects of SGLT2 inhibition.[70] Furthermore, it is noteworthy that increased risk of diabetic ketoacidosis (DKA), an off-target adverse effect of these drugs, has been reported in some randomized controlled trials.[71, 72] Although the risk of DKA is rather low, it is necessary to pay attention to monitoring the level of ketones when doctors consider these agents for their patients.[73] Timely recognition and appropriate management are also of great significance when patients present with vague symptoms. In addition, compared to monotherapy, combination therapies with SGLT2 inhibitors and other anti-diabetic drugs are preferred in clinical practice. Internists are supposed to be careful of the increased risk of hypoglycaemia in the setting of combination treatment. In conclusion, SGLT2 inhibitors would be a promising option for the treatment of DKD.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare. This article does not contain any studies with human participants or animals performed by any of the authors.

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