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A Role for Sodium-Glucose Cotransporter 2 Inhibitors in the Treatment of Chronic Kidney Disease: A Mini Review

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Abstract
Background: Sodium-glucose cotransport protein 2 (SGLT2) inhibitors, a new type of glucose-lowering drug, have been well proved in several clinical studies for their glucose-lowering and nephroprotective effects, and the nephroprotective effects include both indirect effects of metabolic improvement and direct effects, independent of glucose-lowering effects. ***Summary:*** In patients with diabetic kidney disease (DKD), several studies have demonstrated the potential nephroprotective mechanisms of SGLT2 inhibitors, and evidence of nephroprotective mechanisms in the non-DKD population is accumulating. Although the nephroprotective mechanism of SGLT2 inhibitors has not been fully elucidated, several laboratory studies have illustrated the mechanism underlying the effects of SGLT2 inhibitors at various aspects. ***Key Messages:*** The purpose of this article is to review the mechanism of nephroprotective effect of SGLT2 inhibitors and to look forward to promising research in the future.

Introduction

Chronic kidney disease (CKD) affects 697.5 million people globally, with more than 1 million people dying from CKD-related diseases each year. The incidence of CKD is on the rise, given the aging population and increasing prevalence of diseases such as diabetes and hypertension [1]. CKD often remains asymptomatic in the majority of cases until it is advanced, thus frequently remaining undetected and overlooked. Consequently, late referrals and inadequate diagnoses and treatments represent missed opportunities for proper management of CKD and delaying its progression toward kidney failure. Indeed, people with CKD have a much higher risk of death rather than kidney failure since they pay a severe toll in terms of increased cardiovascular disease [2, 3]. Diabetic kidney disease (DKD) is a form of CKD caused by diabetes mellitus with a complex pathogenesis, which is characterized by a persistent increase in albuminuria excretion and/or a progressive decrease in glomerular filtration rate (GFR), ultimately leading to end-stage renal disease (ESRD). DKD is the main cause of ESRD, and approximately 30–50% of ESRD worldwide is caused by DKD [4], and DKD has become the leading cause of ESRD in middle-aged and elderly people [5]. For a better summary, we will provide an overview of both DKD and non-DKD (NDKD) aspects, respectively.

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Sodium-glucose cotransporter 2 (SGLT2) inhibitor, a novel class of hypoglycemic agents, ameliorates hyperglycemic conditions by curtailing renal glucose reabsorption, thus enhancing urinary glucose excretion. Its substantial hypoglycemic efficacy has been validated in numerous clinical studies [6]. Conventional therapies for DKD include glycemic and blood pressure control, inhibition of the renin-angiotensin-aldosterone system, antioxidant, anti-inflammatory, and antifibrotic treatments. However, these therapeutic measures have limited effect in delaying kidney injury, and newer and more effective therapeutic agents need to be found. Currently, dapagliflozin, empagliflozin, and canagliflozin have been approved in several countries for the treatment of adult patients with type 2 diabetes mellitus (T2DM) and heart failure with reduced ejection fraction. Several completed large randomized controlled trials (DECLARE-TIMI 58, EMPA-REGOUTCOME, CANVAS Program and CREDENCE) have confirmed that SGLT2 inhibitors not only reduce glycemia but also have cardiovascular and renal protective effects in patients with T2DM [6–10]. Among them, the CREDENCE study showed that canagliflozin significantly reduced the composite incidence of primary endpoint events in patients with CKD accompanied with T2DM, which included ESRD, doubling of serum creatinine levels, and renal or cardiovascular causes of death [7]. In addition, SGLT2 inhibitors may provide additional renal protection that is independent of the glucose-lowering effect. Of interest, the results of the DAPA-HF study [11] and the DAPA-CKD study [12] suggest that dapagliflozin not only reduces the risk of cardiac and renal events in diabetic patients but also has a protective effect on the prognosis of heart failure and the progression of CKD in non-diabetic patients. Although the specific mechanisms underlying the nephroprotective effects of SGLT2 inhibitors are not fully clarified, many studies in recent years have attempted to elucidate the mechanism of effects from a variety of perspectives.

In this review, we will outline the current research progress of SGLT2 inhibitors in DKD and NDKD in respect to the mechanism of nephroprotection and look forward to the future research of SGLT2 inhibitors in CKD.

SGLT2 and SGLT2 Inhibitors

SGLT belongs to the human solute carrier protein family and is mainly responsible for the transport of glucose, salt ions, vitamins, and short-chain fatty acids. Among them, SGLT1 and SGLT2 play a major role in renal glucose reabsorption. SGLT2 locates in the S1 segment of the renal proximal tubule and accounts for 80–90% of renal glucose reabsorption, while the remaining 10–20% is reabsorbed by SGLT1 in the S3 segment of the renal proximal tubule. SGLT2 inhibitors reduce the reabsorption of glucose by inhibiting SGLT2 of the renal proximal tubule, leading to a decrease in the renal glucose threshold and prompting the excretion of glucose through the urine. Various clinical studies such as VERTIS CV, SCORED, EMPEROR-Preserved, EMPEROR-Reduced, EMPA-KIDNEY, CREDENCE, CANVAS, DELIVER, DAPA-CKD, DAPA-HF, and DECLARE-TIMI 58 have confirmed the hypoglycemic effect and cardiovascular safety of SGLT2 inhibitors [8, 10, 13–21]. In each study, the effect of SGLT2 inhibitors on renal outcomes is presented for the whole trial population and summarized in Figure 1. In addition, SGLT2 inhibitors may have a nephroprotective effect by reducing sodium reabsorption, increasing the concentration of sodium ions flowing through the dense spots, restoring normal tubulo-globular feedback, constricting the small inlet arteries, and reducing hyperfiltration. The CREDENCE study, in which renal outcomes were the primary endpoint, showed that canagliflozin reduced the relative risk of ESRD, doubling of creatinine levels, and mortality caused by nephropathy; the DAPA-CKD study also confirmed the renal benefit of dapagliflozin [13, 14]. Various classes of SGLT2 inhibitors are represented, mainly including canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, and ertugliflozin. Although different classes of SGLT2 inhibitors have shown nephroprotective effects in clinical studies, differences in the molecular structure of drugs and in the degree of selectivity for SGLTs and in the efficacy of SGLT2 inhibition may lead to differences in specific mechanisms of action [22]. Sotagliflozin is the first dual inhibitor with inhibitory effects on both SGLT1 and SGLT2, and the SCORED study was a large, double-blind, placebo-controlled trial that included more than 10,000 patients with CKD (eGFR of 25–60 mL/min/1.73 m^2) and T2DM with concomitant cardiovascular disease risk. It was found that sotagliflozin was significantly effective in reducing the risk of cardiovascular events but was not detected to be nephroprotective compared to placebo [21]. Accordingly, we summarized information regarding the pharmacology, clinical applications, dose adjustment in patients with renal insufficiency, and SGLT2/SGLT1 selectivity with respect to common SGLT2 inhibitors (Table 1).

Remarkably, the use of SGLT2 inhibitors in patients with type 1 diabetes mellitus (T1DM) is currently widely considered to be contraindicated [23]. However, there are

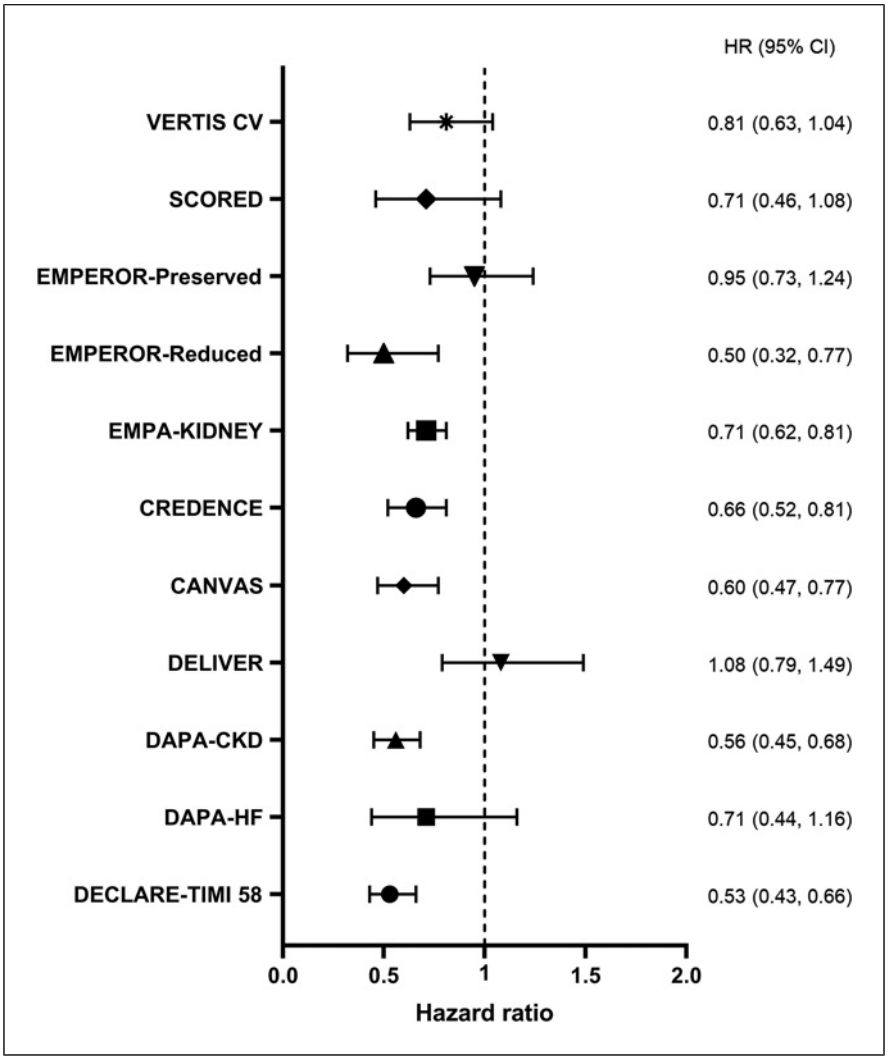

Fig. 1. Incidence of the composite renal outcome in patients treated with SGLT2 inhibitors. A 95% confidence interval (CI) is depicted.

some special considerations for patients suffering from CKD combined with T1DM [24–26]. First, due to the unique role of SGLT2 inhibitors in reducing kidney burden, regulating blood glucose levels, and improving metabolic disorders. On the other hand, some SGLT2i (e.g., dapagliflozin) are available for non-diabetic nephropathies as well, and even the therapeutic indication for CKD was approved by the FDA [27]. As a result, several studies and clinical reports have suggested that the use of SGLT2 inhibitors may be feasible in the setting of a double burden of CKD and T1DM. However, it is worth noting that additional clinical evidence is still needed to ensure the safety and efficacy. Therefore, the decision to administer SGLT2 inhibitors in patients with T1DM combined with CKD should be made cautiously based on the professional judgment of physicians and the recommendations of clinical guidelines.

The Action Mechanism of SGLT2 Inhibitors in DKD

The results of randomized controlled clinical trials related to SGLT2 inhibitors have driven a paradigm shift in the treatment of patients with diabetes. It has been shown that SGLT2 inhibitors not only improve metabolic control but also reduce the progression of CKD in these patients. The magnitude of the nephroprotective effects observed in these studies probably makes SGLT2 inhibitors the most influential class of drugs for the treatment of diabetic patients with CKD since the discovery of inhibitors of the renin-angiotensin system. More strikingly, SGLT2 inhibitors also decelerate the progression of CKD in non-diabetic patients with proteinuria of different extents, suggesting that the mechanism of action of SGLT2 inhibitors is closely related to the pathogenesis of CKD (Fig. 2). Additional to

Table 1. Pharmacology of current SGLT2 inhibitors used in CKD

	Empagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin	Sotagliflozin
Bioavailability (%)	78	78	65	100	70
T_{max} (h)	1–2	2	1–2	0.5–1.5	2
V_d (L)	73.8	118	83.5	86	N/A
PPB (%)	86	98	99	93	N/A
Metabolism	UGT1A3/UGT1A8/ UGT1A9/UGT2B7	UGT1A9	UGT1A9/UGT2B4/ CYP3A4	UGT1A9/ UGT2B7/CYP3A4	UGT1A1/UGT1A9/ UGT2B7/UGT3A4
Unchanged urinary excretion (%)	11–19	2	1	1.5	57
$T_{1/2}$ (h)	10–13	12	11–13	17	21–35
SGLT2/SGLT1 (IC_{50})	3:8,300	1:1,400	3:700	1:2,253	1:20
Benefits for DKD patients	+++	+++	+++	±	±
Recommended dose in CKD	eGFR >30, no dosage adjustment eGFR 20–29, 10 mg daily	eGFR >25, no dosage adjustmen	eGFR 30-59, 100 mg daily eGFR <30, off label, 100 mg daily	No dosage adjustment	eGFR >25, no dosage adjustment

+++ represents highly beneficial, HR ≤0.75.

hyperglycemia, which is the initiating factor in the development and progression of DKD, hypertension, altered tubular-globular feedback, hypoxia, tubular hypertrophy, podocyte injury, proteinuria and lipotoxicity, endothelial dysfunction, mitochondrial damage, inflammation, fibrosis, and impaired autophagy also drive the progression of DKD [28]. The current study shows that SGLT2 inhibitors may exert nephroprotective effects by mediating the above pathogenic mechanisms.

Modification of Glucose Metabolism Disorders

SGLT2 inhibitors are used to reduce blood glucose by lowering the renal glucose threshold. Empagliflozin has demonstrated significant hypoglycemic effects in *ob/ob* mice, a model of spontaneous T2DM, and significantly improves the early characteristics of DKD in BTBR *ob/ob* mice with and without hypertension [29]. Disorders of glucose metabolism play an important role in the development of DKD, and SGLT2 inhibitors can restore the normal glucose metabolism. In BTBR *ob/ob* diabetic mice, ipragliflozin reduces blood glucose and effectively decreases the levels of citric acid, an intermediate product of the tricarboxylic acid cycle that accumulates in the kidney, and the levels of oxidative stress [30]. Another study conducted at the animal level showed that empagliflozin normalized silent information regulator 3 (SIRT3) levels and abnormal glycolysis in the kidney of streptozotocin-induced CD-1 diabetic mice, as evidenced by hypoxia inducible factor-1α (HIF-1α) accumulation, activation of hexokinase 2, and pyruvate kinase isozyme M2 dimer formation. Empagliflozin also inhibits the accumulation of glycolytic byproducts in the kidney, and canagliflozin also normalizes glycolysis in mice [31]. In vitro studies have demonstrated that canagliflozin can prevent the abnormal activation of the glycolytic pathway in renal tubular epithelial cells under high-glucose conditions and exert nephroprotective effects by inhibiting the formation of mitochondrial reactive oxygen species clusters and the transcription of secreted phosphoprotein 1 and the overexpression of renal tubular-specific inositol oxygenase [32].

Lower Blood Pressure

Hypertension is a common complication or comorbidity of diabetes mellitus, and about 60% of patients with T2DM are accompanied by hypertension [33]. Renal disease progresses more slowly in DKD patients with normal blood pressure compared to those with hypertension, and thus hypertension is a major factor in the progression of DKD. A randomized, double-blind, placebo-controlled phase 3 study showed that dapagliflozin was effective in lowering blood pressure and that adding dapagliflozin to conventional antihypertensive agents further lowered blood pressure [34]. The findings after treatment of New Zealand obese T2DM mice induced by a high-fat diet with canagliflozin showed that canagliflozin prevented intrarenal angiotensinogen elevation and improved renal injury and hypertension in

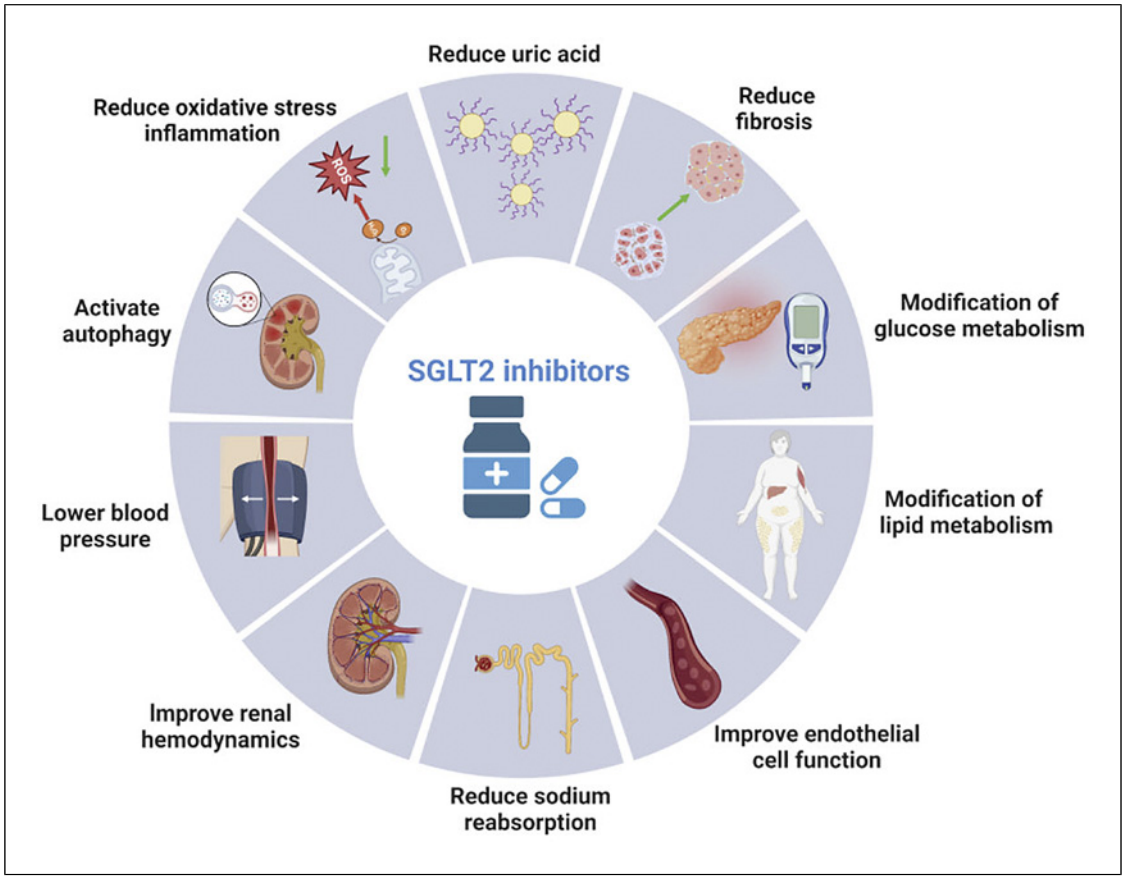

Fig. 2. Primary mechanisms of SGLT2 inhibitors decelerating development of CKD. Created with BioRender.com.

mice [35]. In a conscious rabbit model of diabetes, empagliflozin restored diabetes-induced renal sympathetic nerve activity and pressure-receptive reflexes to lower blood pressure, suggesting that inhibition of sympathetic nerve activity may be a cause of blood pressure reduction by SGLT2 inhibitors [36].

Improve Renal Hemodynamics

Early renal hemodynamic alterations in DKD present as glomerular hyperperfusion and hyperfiltration. SGLT2 inhibitors restore sodium delivery to dense spots and improve hemodynamics by causing constriction of the small incoming glomerular arteries and dilation of the small outgoing glomerular arteries through tubular-globular feedback, improving glomerular hyperperfusion, high pressure, and hyperfiltration. Vallon et al. [37] demonstrated that empagliflozin reduced or prevented increased GFR, proteinuria, increased glomerular volume, and inflammation. A randomized double-blind trial [38] in patients with T2DM showed that dapagliflozin resulted in a dramatic decrease in GFR accompanied by a decrease in renal blood flow and renal vascular resistance, which confirmed that the nephroprotective effect of SGLT2 inhibitors is achieved, at least in part, through direct renal hemodynamic effects.

Reduce Uric Acid

Uric acid has been recognized as an independent risk factor for DKD. Notably, the presence of hyperuricemia in patients with T2DM is associated with a significantly elevated incidence of DKD. Studies have shown that the decrease of blood uric acid in healthy subjects after oral administration of luseogliflozin is caused by increased uric acid excretion, and further cellular experimental studies suggest that luseogliflozin may stimulate uric acid excretion mediated by glucose transporter 9 subtype 2 or other renal tubular transporter proteins by increasing glucose concentration in the renal tubular lumen and decrease serum uric acid levels through inhibiting uric

acid reabsorption mediated by glucose transporter 9 subtype 2 [39, 40]. However, the precise mechanism through which SGLT2 inhibitors exert their hypouricemic effect on the kidney remains to be fully elucidated.

Reduce Sodium Reabsorption

The mechanisms of sodium reabsorption in the kidney are complex. In addition to SGLT2, the Na^+-H^+ exchanger (NHE) at the proximal tubule, the Na^+-K^+-$2Cl^-$ cotransporter at the thick segment of the ascending branch of the medullary collaterals, and the Na^+-Cl^- cotransporter at the distal tubule are also important transporters. The major part of sodium reabsorption in the proximal tubule of diabetic patients is mediated by the increased expression and activity of NHE3, and interestingly, SGLT2 and NHE3 are co-localized and functionally intertwined in the early proximal tubule. SGLT2 inhibitors may interact with NHE3 by inhibiting SGLT2 [41]. SGLT2 inhibitors improved glomerular hyperfiltration by interfering with NHE3 in the proximal tubule, increasing sodium delivery to the macular densities and delaying the progression of kidney disease in a pathway independent of blood glucose and urine glucose, and enhanced AMP-activated protein kinase (AMPK)/SIRT1 signaling may also be involved in the role of SGLT2 inhibitors in affecting sodium transport mechanisms [42, 43]. Overall, SGLT2 inhibitors can affect sodium reabsorption by modulating the activity of other sodium transporters.

Improve Hypoxia

The kidney oxygen consumption is primarily driven by the metabolic demand generated by sodium reabsorption in the renal tubules, and the activity of SGLT2 will significantly increase oxygen depletion. The reabsorption of sodium and glucose in the proximal tubule of the kidney is significantly increased in the hyperglycemic state, and SGLT2 is upregulated, causing increased oxygen consumption that predisposes the kidney to hypoxia. Hypoxia, in turn, promotes the expression of HIF-1α, which will further aggravate renal injury; SGLT2 inhibitors can reduce oxygen consumption and alleviate renal hypoxia by inhibiting SGLT2 [44]. Luseogliflozin and dapagliflozin could slow down the impairment of renal function, attenuate the markers of tubular injury, reduce tubular interstitial fibrosis, and modulate the tubular response to hypoxia by reducing high-glucose-induced O-linked N-acetylamino-glucose glycosylation modifications via the HIF pathway [45, 46]. Therefore, the nephroprotective effect of SGLT2 inhibitors may involve the inhibition of HIF-1α.

Modify Disorders of Lipid Metabolism

Disturbances in lipid metabolism are evident early in DKD, and patients with DKD have significant lipid deposition in the small renal arteries, glomeruli, and tubules. Several studies have reported a reduction in triglycerides and total cholesterol after SGLT2 inhibitor treatment; however, there is controversy regarding the observed changes in serum levels of HDL cholesterol and LDL cholesterol [47]. DKD patients have impaired fatty acid utilization and lipid accumulation in the proximal tubule, which is associated with increased expression of HIF-1α, and dapagliflozin exerts its protective effect on correcting lipid metabolism by inhibiting HIF-1α in renal tubular epithelial cells [48].Tomita et al. [49] reported that the nephroprotection of empagliflozin was produced by elevation of endogenous ketone bodies that deletion of the ketone synthesis rate-limiting enzyme HMGCS2 gene abolished its nephroprotective effect, and that elevation of ketone bodies in turn acted on the kidneys of non-proteinuric and proteinuric DKD mice to inhibit mammalian target of rapamycin complex 1 (mTORC1) overactivation, thereby protecting renal function. SIRT1/peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α)/fibroblast growth factor 2 (FGF21) are major regulators of nutrition and intracellular homeostasis, and all three promote gluconeogenesis, fatty acid oxidation, and ketogenesis. The use of SGLT2 inhibitors can protect renal function by activating SIRT1/PGC-1α/FGF21, promoting ketone body production and promoting autophagy [50]. Furthermore, in addition to restoring glomerular feedback and improving proximal renal tubular oxygenation, SGLT2 inhibitors may exert nephroprotective effects by elevating circulating levels of β-hydroxybutyrate and inhibiting oxidative stress, inflammation, and fibrosis, rather than by increasing ketone body oxidation [51].

Reduce Oxidative Stress, Inflammation, and Fibrosis

In DKD, there is a significant increase in oxidative stress on the kidney, which can promote renal inflammation and fibrotic injury via several pathways. SGLT2 inhibitors can intervene in these mechanisms, thereby exerting nephroprotective effects [52]. The expression of high-mobility group box 1 is increased in DKD patients, which upregulates the expression of the receptor for advanced glycation end products, and nuclear factor-1 κB. On the contrary, dapagliflozin inhibited the high-mobility group box 1/receptor for advanced glycation end products/nuclear factor-1 κB signaling pathway in HK-2 cells and significantly reduced the levels of inflammatory markers, thereby delaying the progression of renal injury

[53, 54]. In summary, SGLT2 inhibitors have the potential to alleviate oxidative stress, improve cellular and tissue inflammation, and renal tubular interstitial fibrosis in the context of diabetic kidney by acting through multiple pathways.

Activate Autophagy

Autophagy is a lysosome-mediated degradation pathway that is essential for cellular homeostasis. Autophagy deficiency plays a key role in the pathogenesis of glomerular and tubular pathology in DKD. Empagliflozin increases the expression of the glomerular autophagy marker Beclin-1 and lysosome-associated membrane protein 1, increases the bulk density of autophagic vesicles, lysosomes, and autophagic lysosomes and decreases the expression of apoptotic markers in T2DM mice [55]. The AMPK/SIRT1 signaling pathway stimulates autophagy and maintains intracellular homeostasis of the kidney, and defects in this pathway are associated with the development of DKD. SGLT2 inhibitors can induce both AMPK and SIRT1, thereby improving cellular stress, stimulating autophagy, and reducing glomerular and tubular injury [42].

Improve Endothelial Cell Function

Glomerular endothelial cells are layer 1 of the glomerular filtration barrier. The endothelial cell is in direct contact with the blood circulation, and it is not only directly damaged by the effects of high perfusion, hyperfiltration, and hyperpressure within the glomerulus but also by changes in the blood composition of patients with DKD. Studies in the laboratory have shown that glomerular endothelial cells in patients with DKD have a decreased ability to synthesize glycoproteins, and that hyperglycemia promotes endothelial cell death, inhibits endothelial cell proliferation, and prolongs the time to reach full fusion of endothelial cells cultured in vitro [56]. In DKD, glomerular endothelial cells undergo necrosis or apoptosis and are detached from the basement membrane into the circulatory system, leading to a reduction in the number of glomerular endothelium and impaired endothelial integrity, which is an important process in the formation of proteinuria. Empagliflozin and dapagliflozin could attenuate tumor necrosis factor α (TNFα)-induced endothelial inflammation, furthermore increase NO bioavailability and inhibit TNFα-induced reactive oxygen species production, exerting improved endothelial cell function [56, 57]. Canagliflozin reduced vascular smooth muscle cells (VSMCs) proliferation and migration in a concentration-dependent manner [58, 59]. Meanwhile, empagliflozin and dapagliflozin had similar effects on the proliferation and migration of VSMCs [57–59]. In this regard, the vascular effects of SGLT2 inhibitors by improving endothelial cell function and regulating the proliferation and migration of VSMCs was an important mechanism for exerting a preventive effect for DKD.

Others

In addition to the classical pathogenic mechanisms described above, excessive mitochondrial division is also present in DKD, and studies in the KK-Ay diabetic mouse model have demonstrated that empagliflozin and ipragliflozin may ameliorate diabetic tubular damage by attenuating mitochondrial division through the AMPK/specific protein 1/phosphoglycerate translocase 5 pathway [60, 61]. Empagliflozin ameliorates renal injury in diabetic mice by inhibiting the NOD-like receptor protein 3/cysteine protease-1/Gasdermin-D cell scorch-signaling pathway [62]. However, the effect of different classes of SGLT2 inhibitors on renal gluconeogenesis is variable. It has been shown that dapagliflozin does not alleviate but rather aggravates DKD, as evidenced by microalbuminuria, elevated blood urea nitrogen levels, and glomerular and tubular damage in *db/db* mice, probably due to increased urinary glucose excretion and hepatic gluconeogenesis, which exacerbates renal injury by increasing the expression levels of forkhead transcription factor O1 in the kidney and liver that induces the expression of key rate-limiting enzymes for gluconeogenesis [63, 64].

Clinical Evidence for the Role of SGLT2 Inhibitors in NDKD

Clinical trials have shown that SGLT2 inhibitors delay the progression of nephropathy and reduce cardiovascular and renal endpoint events in CKD patients without complication of diabetes [15, 65, 66]. To test the hypothesis that the nephroprotective effect of SLGT2 inhibitors extends to non-diabetic patients with CKD, the DAPA-CKD trial, a randomized, double-blind, controlled, multicenter study of dapagliflozin enrolling 4,304 diabetic and non-diabetic patients with CKD, was designed. The results of the DAPA-CKD trial demonstrated that based on standard treatment, dapagliflozin significantly reduced the risk of renal and cardiovascular events and all-cause mortality among the primary endpoints in subjects compared with placebo [65, 67]. In subgroup stratified analyses, the benefit of dapagliflozin in the risk of renal and cardiovascular adverse events and all-cause mortality was comparable between races and between

those with estimated GFR (eGFR) >45 mL·min^{-1}·(1.73 m^2)$^{-1}$ versus ≤45 mL·min^{-1}·(1.73 m^2)$^{-1}$ in patients of CKD with or without T2DM [65, 67, 68]. In further subgroup stratification analyses of different CKD pathologies, dapagliflozin consistently reduced renal and cardiovascular adverse events, slowed the decline in eGFR, and reduced urinary albumin in patients with IgA nephropathy. In contrast, in patients with focal segmental glomerulosclerosis, dapagliflozin slows the decline in eGFR and reduces urinary albumin [69, 70].

The EMPA-KIDNEY trial recruited 6,609 patients with CKD who were receiving contextual ACEi/ARB therapy, inclusively 3,569 subjects without diabetes [20]. The study was discontinued with a median follow-up of 2 years because empagliflozin showed significant efficacy in lowering the progression of nephropathy and cardiovascular death, and the drug effects were similar in diabetic and non-diabetic patients. The EMPA-KIDNEY trial also showed that subjects with severe CKD (eGFR of 20–30 mL/min/1.73 m^2) could also benefit after receiving treatment with empagliflozin. According to earlier clinical evidence, the use of SGLT2 inhibitors for nephroprotection in diabetic patients was not associated with urinary protein levels at baseline [71]. As a consequence, though, in the EMPA-KIDNEY trial, the benefit was greater in patients with more elevated levels of UACR (the risk reduction was 23% in patients with a UACR >300 mg/g, 9% in patients with a UACR 30–300 mg/g).

The DAPA-HF trial, on the other hand, was specifically designed to clarify whether the treatment was equally effective in patients with HF (both in patients with 2 diabetes mellitus and in patients without diabetes mellitus), more than half of whom did not have combined diabetes mellitus [15]. The DAPA-HF study included patients with 2–4 heart failure with an ejection fraction of less than 40%; the primary endpoints of the study were death and worsening heart failure due to cardiovascular events and the secondary endpoints were worsening renal function, including eGFR decline of more than 50%, ESRD, maintenance dialysis, and renal death. The results of this study showed that dapagliflozin significantly reduced the cardiac composite endpoint by 26% and had the same benefit in non-diabetic patients. The effect of dapagliflozin on the composite endpoint of worsening renal function did not differ from placebo, but significantly reduced the elevation of blood creatinine.

The DIAMOND study [66] included patients with CKD without T2DM and combined with proteinuria, and the primary endpoint was the change in 24-h urinary protein levels. After 6 weeks of treatment with dapagliflozin, there was a reversible decrease in the measured GFR with a significant weight loss. This suggests that renal hemodynamic changes in patients with NDKD on SGLT2 inhibitors may be similar to those in patients with DKD.

The Recognition, Prevention, and Management of Adverse Drug Reactions to SGLT2 Inhibitors

Adverse drug reactions that need to be considered in the clinical use of SGLT2 inhibitors include: kidney impairment, genital and urinary tract infections, euglycemic diabetic ketoacidosis (EDKA), amputation of extremities, hypoglycemia, hypotension. A transient decrease in eGFR, defined as a decline in eGFR of >10% from baseline within 4 weeks, may occur in patients initiating SGLT2 inhibitors, and should be differentiated from acute kidney injury, which usually does not need to be treated [72]. If the decline in eGFR is substantial (>30% from baseline), then vigilance and dose adjustment is warranted. Therefore, eGFR needs to be monitored at least 4 weeks after initiating treatment with SGLT2 inhibitors. There is an increased risk of developing genital and urinary tract infections due to increased glucose levels in the urine with SGLT2 inhibitor therapy. Prior to the use of SGLT2 inhibitors, risk factors for triggering infections need to be assessed, and the use of SGLT2 inhibitors is not recommended for patients with recurrent genitourinary infections within 6 months. Patients should be recommended to pay attention to urogenital hygiene and adequate flushing [73]. During the use of SGLT2 inhibitors, patients need to be carefully monitored for symptoms of infection (urinary frequency, urgency, painful urination, etc.). If infection occurs, it is recommended that SGLT2 inhibitors be suspended and specialist treatment given. EDKA is characterized by mild hyperglycemia (<250 mg/dL), ketosis, and metabolic acidosis. During the administration of SGLT2 inhibitors, if a patient develops symptoms associated with EDKA such as abdominal pain, nausea, vomiting, malaise, and dyspnea, it is necessary to consider whether the patient is experiencing EDKA and to promptly perform blood, urine ketone body, and arterial blood gas analyses to make a definitive diagnosis. Once EDKA is diagnosed, discontinue the use of SGLT2 inhibitors. Treatment with canagliflozin increased the risk of amputation in the CANVAS study, but it has not been confirmed in other studies whether the treatment with SGLT2 inhibitors is associated with amputation. Prudent use of SGLT2 inhibitors is recommended for patients with risk factors for amputation, especially those with a previous history of

amputation or foot ulcers, neuropathy, or peripheral vascular disease [74]. Hypoglycemia is a common adverse drug reaction of hypoglycemic agents; however, SGLT2 inhibitor monotherapy is not typically associated with an increase in hypoglycemic events. Hypoglycemia may occur when SGLT2 inhibitors are combined with sulfonylureas or insulin [75]. SGLT2 inhibitors induce osmotic diuresis and can cause hypotension in susceptible patients. The volume status of the patient should be assessed prior to initiating SGLT2 inhibitors. Precaution should be exercised when initiating SGLT2 inhibitors in patients with decreased renal function, in the elderly, and in patients with low baseline systolic blood pressure.

Future Perspectives

Given the complex pathogenesis of DKD, the nephroprotective mechanism of SGLT2 inhibitors has not been completely uncovered, warranting further exploration. Despite various kinds of SGLT2 inhibitors have shown similar mechanisms of action in numerous studies, the effects on renal gluconeogenesis have varied. Therefore, an in-depth exploration of the differences in the renal protective mechanisms of various kinds of SGLT2 inhibitors will provide a more solid basis for individualized drug use and precise treatment. Addition to DKD, SGLT2 inhibitors also have good cardio-renal protective effects in NDKD patients and have more extensive potential for clinical application in the treatment of CKD. Dapagliflozin has been approved by the US Food and Drug Administration for use in patients with CKD, and the EMPA-KIDNEY study provides further evidence for the use of SGLT2 inhibitors for cardiac and renal protection in patients with NDKD. The mechanisms of nephroprotection of SGLT2 inhibitors independent of glucose lowering are diverse and need to be elucidated by more basic and clinical studies.

Recent research has illuminated a compelling proposition: the renoprotective potency of SGLT2 inhibitors within glycogen storage diseases, particularly in curbing renal glycogen accumulation [76–78]. This avenue invites us to explore the versatile and promising applications of SGLT2 inhibitors in advancing renal health. Glycogen storage diseases encompass a range of hereditary metabolic disorders like Pompe disease and McArdle disease, marked by enzymatic deficits fostering anomalous glycogen buildup, predominantly in organs such as the liver and muscles. Notably, renal glycogen accrual holds the potential to detrimentally affect kidney function. In this vista, by intervening in renal tubular SGLT2 functionality, SGLT2 inhibitors augment glucose elimination, thereby attenuating renal glycogen accumulation in glycogen storage disease patients [79, 80]. Given the pivotal significance of this observation, further delving into the renoprotective implications of SGLT2 inhibitors in the context of glycogen storage diseases promises to unfurl extensive avenues for future research and clinical applications.

Clinical and mechanistic studies suggest that dapagliflozin has a nephroprotective effect independent of metabolic improvement, suggesting that its nephroprotective effect comes from the indirect effect of improving metabolic problems such as blood glucose, blood pressure, and blood uric acid on the one hand, and on the other hand, its nephroprotective effect may have other direct targets. In vitro studies have demonstrated that dapagliflozin has the beneficial effect of improving glomerular podocyte function, but podocytes do not express the classical target (SGLT2). No studies related to direct nephroprotective targets have ever been reported, which is of great value in advancing the understanding and application of this class of drugs in the treatment of CKD, and deserves further exploration.

Conclusions

SGLT2 inhibitors have exhibited nephroprotective activities in both clinical and basic studies. Their incorporation into therapeutic strategies has the potential to revolutionize the treatment of DKD. Further exploration of their nephroprotective mechanisms may pave the way for broader applications of SGLT2 inhibitors in NDKD.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.S. wrote the manuscript. J.N. and X.L. revised the manuscript. All authors reviewed, considered, and approved the manuscript.

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