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Review

The major molecular mechanisms mediating the renoprotective effects of SGLT2 inhibitors: An update

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ABSTRACT

The incidence of diabetes mellitus, as well as its complications, is rapidly growing. Diabetic nephropathy is one of the most prevalent disorders induced by chronic uncontrolled hyperglycemia and is accompanied by a reduction in renal sufficiency with microstructural tissue damage in the kidneys. Many therapeutic protocols have been designed to address the treatment and prevention of diabetic nephropathy. Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are a newly introduced class of glucose-lowering agents that reduce blood glucose by inhibition of urinary glucose reabsorption in renal proximal tubules and so induce glycosuria. Also, these hypoglycemic agents may provide protective effects in different tissues such as cardiovascular, brain, and kidneys. In recent years, accumulating evidence has indicated that SGLT2i possess potent renal protective properties in the setting of diabetes. In the current study, we present the latest findings regarding the renoprotective effects of SGLT2 inhibition and discuss the molecular mechanisms involved.

1. Introduction

The global prevalence of diabetes mellitus (DM) is burgeoning [1]. This metabolic disorder involves disordered metabolism leading to activation of pathologic molecular pathways such as oxidative stress, inflammation and apoptosis [2,3]. Therefore, diabetes impacts most tissues producing undesirable diabetic complications [4,5]. Diabetic nephropathy (DN) is prevalent among diabetic patients and is activated by underlying molecular mechanisms induced by uncontrolled hyperglycemia [6]. DN is also the most prevalent cause of renal failure (from which up to 30% of diabetic patients will suffer) and leads to the need for renal replacement therapy [7,8]. The exact pathophysiology of DN is as yet unclear, but the roles of oxidative damage, inflammatory responses and apoptosis are well recognized [9]. Together with diabetes-induced cardiovascular complications, DN is considered to be the major cause of mortality in patients with uncontrolled diabetes [10]. Hence, many preventive or therapeutic strategies have been developed to improve renal sufficiency in diabetic patients [4,11].

Sodium-glucose cotransporter type 2 inhibitors (SGLT2i) are a newly introduced class of antidiabetic agents which reduce plasma glucose by inhibition of glucose uptake in renal proximal tubules [12–15]. Sodium-glucose cotransporters are mainly located in the brush border of renal proximal tubules and are responsible for re-uptake of filtrated glucose from tubules and returning it to the circulation [12]. Thus, inhibition of these carriers translates into urinary glucose excretion and lower levels of plasma glucose [12]. Therefore, SGLT2i can induce a potent glucose-lowering effect, especially in patients with higher prevailing levels of glycaemia [12]. However, some evidence indicates that these agents can also provide other therapeutic effects, specifically on the kidneys [12]. SGLT2i drugs have been shown to be able to suppress the molecular mechanisms involved in the pathophysiology of DN [8,12]. In the current review, we present the latest findings regarding the renoprotective effects of SGLT2 inhibition and discuss the molecular mechanisms involved.

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2. Classification of diabetes mellitus

DM has been traditionally categorized into three main types as type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes [16]. Nonetheless, a novel diabetes classification (based on glutamate decarboxylase antibodies, age at diagnosis, body mass index, HbA1c, insulin resistance, and β-cell function) has recently been proposed including 5 subgroups: severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes and mild age-related diabetes [17]. T1D accounts for approximately 5–10% of all diabetic subjects and is due to autoimmune-mediated beta-cell destruction resulting in insufficient insulin production from residual beta cells and low circulating insulin levels [16]. T2D is the most prevalent type of diabetes, accounting for 90–95% of diabetic subjects, and is due to inadequate insulin secretion combined with insulin resistance [16]. Gestational diabetes is another type of DM which develops in pregnant women, usually resolves post-delivery, and is due largely to hormonal variations during pregnancy [18]. Severe autoimmune diabetes overlap with T1D and latent autoimmune diabetes in adults (LADA), severe insulin-deficient diabetes and severe insulin-resistant diabetes (SIRD) are two severe forms of T2D accounting for 10–20% and 10–17% of diabetic subjects respectively, while the most prevalent subgroup is mild-age-related diabetes (35–47%) [17]. The risk of DN is particularly increased in the SIRD subgroup, thus highlighting a major role of insulin resistance in diabetic kidney diseases.

3. Pathophysiology of diabetic nephropathy at a glance

DN has a complicated pathophysiology [19,20]. Although its exact underlying cause is still unclear, activation of many molecular pathways is involved; these include oxidative stress [3], endoplasmic reticulum stress [21], glomerular hyperfiltration [22], inflammation [23], innate immunity [24], the renin-angiotensin system (RAS) [25], transforming growth factor-β (TGF-β) [26], protein kinase C (PKC) [25], tumor necrosis factor-α (TNF-α) [25], nuclear factor kappa-b (NF-κb) [27], adhesion molecule up-regulation [28], and apoptotic pathways [9]. Hemodynamic variation and intraglomerular hypertension are additionally responsible for the renal tissue injuries induced by chronic uncontrolled hyperglycemia [29]. Insulin resistance is associated with many of these mechanisms, such as glomerular hypertension, hyperfiltration, and inflammation [30]. Accordingly, the prevalence of DN has been reported to be high in the SIRD cluster of patients, with severe insulin resistance [20]. Those patients showed overall an adequate metabolic control, thus suggesting that other than hypoglycemic mechanisms are required for renoprotection [17].

4. SGLT2 inhibitors

SGLT2 inhibitors are a group of glucose lowering drugs that inhibit glucose tubular reabsorption and induce its urinary excretion by reduction of the renal glucose threshold [12,31]. This class of hypoglycemic drugs works completely independent of the insulin hormone and functions according to the prevailing serum glucose level, thereby carrying a negligible risk for hypoglycemia [32]. After the discovery of phlorizin as the first SGLT inhibitor, several formulations of SGLT2 inhibitor have been introduced [32,33]. These antidiabetic agents reduce plasma glucose by decreasing renal tubular glucose reabsorption [34,35]. In addition to their potent hypoglycemic effects, they may also exert other effects, such as weight loss [36], decreased blood pressure [37], reduced uric acid levels [38], attenuation of oxidative stress [39], anti-inflammatory action [40], and improve fibrosis [40], SGLT2 inhibitors may, however, be accompanied by side effects, such as dehydration, dizziness and fainting, hypotension and urinary tract infections [41]. Canagliflozin, dapagliflozin, and empagliflozin are approved SGLT2i in widespread clinical use [41].

5. Renoprotective effects of SGLT2 inhibition

Although hypoglycemic effects are the initial outcomes of SGLT2i, emerging evidence suggests that these antidiabetic drugs exhibit other pharmacological properties with effective renoprotective effects [42]. These beneficial activities of SGLT2i on renal outcomes may be due to their glucose lowering mechanisms while other renoprotective effects could be independent of them; however, it is not fully understood yet and further detailed studies are needed in this field to elucidate whether the renal protection of SGLT2i is solely explained by their anti-hyperglycemic effects or not. In this regard, it has been well demonstrated that SGLT2i protect kidneys by anti-inflammatory effects via reducing serum levels of leptin and IL-6, increasing adiponectin concentrations, mitigating systemic inflammation through decreasing CRP (C-reactive protein) level, and inhibition the IL-1β secretion by macrophages *via* the ROS-NLRP3-caspase-1 pathway [43–45]. It seems that these anti-inflammatory effects of SGLT2i as well as some other mechanisms such as lowering serum uric acid levels, blood pressure, and glomerular hyperfiltration are independent of their glucose-lowering properties. However, the evidence suggests that these antidiabetic drugs may be considered as both renoprotective and hypoglycemic agents. In this review, we discuss about the possible molecular mechanisms involved in the renoprotective actions of SGLT2i (Table 1).

5.1. Improvement of glycemic control

Hyperglycemia is the most prominent and obvious issue in diabetes, and many subsequent complications are due to elevated serum glucose

Table 1
Major molecular mechanisms mediating the renoprotective effects of SGLT2 inhibitors.

	Mechanisms	Role of SGLT2 Inhibition	Ref.
Renoprotective roles of SGLT2 inhibitors	Improvement of Glycemic Control	Reduction in blood glucose and thereby prevention of glucotoxicity	[8,49,50,51,53]
	Improvement of Hemodynamic Variations	Prevention of hemodynamic changes, readjustment of blood pressure control	[8,52,60,61,62,66,70]
	Induction of Weight Loss	Reduction in body weight and prevention of obesity-related complications	[8,70,73,74]
	Prevent of Oxidative Damages	Amelioration of free radical generation and prevention of downstream consequences including apoptosis	[12,76,77] [78,79,82,83]
	Inhibition of Inflammatory Responses and Fibrotic Processes	Attenuation of inflammatory mediator expression/release, prevention of fibrosis in kidney tissues	[12,93,94,95]
	Reduction of Uric Acid Levels in Plasma	Induction of uric acid urinary excretion	[96,100,101,102,103,104,105]
	Reduction in RAS Activation	Amelioration of RAS activity leading to decreased deleterious outcomes.	[106,109,110]
	Reduction in Natriuretic Peptides	Regulation of natriuretic peptide secretion	[117,121,122]

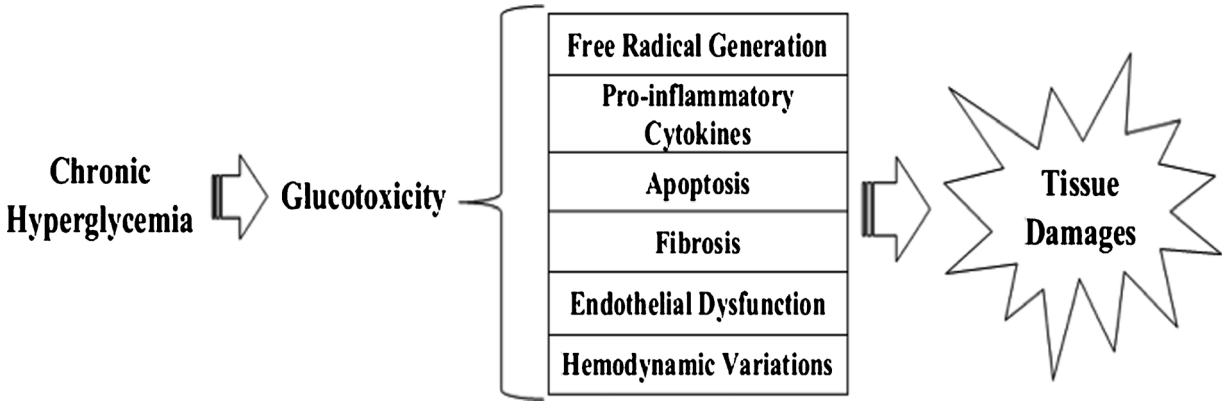

Fig. 1. Mechanisms implicated in tissue damage by chronic hyperglycemia.

concentrations [46,47]. Glucose is a potent inducer of many pathophysiologic pathways, such as oxidative stress, inflammation and apoptosis that are involved in DN and chronic kidney disease (CKD) [2,3,48] (Fig. 1). Therefore, any glucose lowering agent can protect against this "Diabetic Glucotoxicity" and, thereby, prevent hyperglycemia-induced disorders including CKDs [47]. This effect is common across all classes of hypoglycemic drugs, but SGLT2i agents have been proposed to play additional benefits on glucotoxicity in susceptible tissues such as kidneys, the cardiovascular system and the neuronal network [49–51]. In particular, SGLT2 ameliorated oxidative stress, fibrosis and inflammation predominantly in the tubule-interstitium [39,50] and showed a greater efficacy than dipeptidyl peptidase-4 inhibitors in improving hippocampal synaptic plasticity [51].

Aroor et al. in 2018 demonstrated that the hypoglycemic effects of SGLT2i are critically important in reducing renal damage in T2D animal model [52]. Fioretto and colleagues in 2016 reported that the renoprotective properties of SGLT2i are, at least in part, due to an improvement in the glycemic profile [8]. Of note, the hypoglycemic effects of SGLT2is are dependent upon normal kidney function and normal physiological feedback between the renal macula densa and glomerulus [8]. Therefore, SGLT2i may not be as effective in renal failure where the eGFR (estimated glomerular filtration rate) is below 60 mL/min/1.73 m^2 [8,53]. Their action on glucose control is reduced in patients with impaired renal function and their use might be accompanied by side effects [54]. Nevertheless, the beneficial effect of SGLT2i on cardiovascular risk factors such as body weight, blood pressure, and urinary albumin-to-creatinine ratio persists despite renal impairment [55] resulting in renoprotection via non-glucosuric mechanisms. Additionally, because SGLT2is exhibit prominent non-glycemic effects possibly *via* natriuretic/diuretic effects, inhibition of sodium reabsorption in the proximal tubule and downregulation of NHE3 sodium transport activity [55], these antidiabetic drugs could exert their renoprotective activities in nondiabetic patients.

5.2. Reduction in tubular Na+reabsorption and improvement of hemodynamic variations and blood pressure

Diabetes-induced microvascular complications, such as DN, are accompanied by hemodynamic variations and systemic hypertension and, therefore, normalizing blood pressure (BP) is critical in the prevention of CKD in diabetic patients [56,57]. Raised BP potentially reduces renal sufficiency by induction of hyperfiltration and intraglumerular pressure, leading to destruction of the glomerular network at the microvascular level [58,59].

Emerging evidence shows that SGLT2 inhibition improves diastolic and systolic BP control by lowering body weight and via induction of osmotic diuresis that results in hypovolemia [8,60–62]. SGLT2 inhibition decreases sodium reabsorption in the proximal tubules, thereby causing increased sodium delivery to the macula densa in the distal tubule and inducing afferent vasoconstriction by tubuloglomerular feedback leading to lower glomerular hyperfiltration [62,63]. Reduction in BP may also be linked to a decrease in total body sodium content. In this regard, it has been revealed that a significant reduction of skin sodium content following SGLT2i therapy; nevertheless, it is not clear whether the decreased sodium content is a direct effect of these drugs or a consequence of prolonged reduction in renal sodium excretion [64]. It has been hypothesized that SGLT2i may decrease interstitial fluid volume suggesting a potential therapeutic effect in heart failure by reducing congestion without decreasing arterial filling and organ perfusion [65]. SGLT2i use also improves vascular stiffness resulting in increased elasticity and more efficient BP regulation [52,66]. Furthermore, it has been reported that SGLT2is exhibit a slight acute reduction in eGFR and lower albuminuria during treatment [67,68]; however, glomerular hemodynamic changes may be reversed after discontinuation of SGLT2is [69]. Recent results of a large clinical trial (CREDENCE) supported the potential benefits of SGLT2i on kidney and cardiovascular outcomes in diabetic patients at a high risk for developing CKD [42]. SGLT2i used to manage diabetes also improve endothelial function and prevent aortic stiffness by down-regulation of RECK ("reversion inducing cysteine rich protein with Kazal motifs," an anti-fibrotic factor) through inhibition of membrane-anchored matrix metalloproteinase activation resulting in a positive effect of SGLT2i on periarterial fibrosis [52]. Lee et al in 2018 reported that SGLT2 inhibition improves systemic vascular dysfunction by reducing aortic pulse wave velocity and increasing endothelium-dependent dilation leading to decreased stiffness and an improved response to stimuli [66]. In summary, SGLT2 inhibition improves the hemodynamic deviations that occur in CKDs and reduces BP by induction of osmotic diuresis and improvement of endothelial function and vascular tone [52,66,70]. It is noteworthy that these renoprotective effects of SGLT2i are likely independent to their glucose-lowering potencies.

5.3. Induction of weight loss and further consequences

Weight loss during treatment with SGLT2 inhibitors has been consistently observed and it could be a consequence of the calorie deficit induced by glycosuria [71]. A previous meta-analysis revealed that different doses of each SGLT2i agent are associated with significant weight reduction in T2D patients [72]. SGLT2 inhibition can be renoprotective through the reduction in body weight, since many pathological molecular mechanisms involved in CKDs are influenced by adipose tissue [8,70,73]. The SGLT2i-induced reduction in body weight has also been linked to a decrease in triglyceride levels, leading to improved insulin sensitivity [74]. Simply lowering body weight, therefore, decreases the risk factors involved in the pathophysiology of CKD and DN [74]. The weight loss effects of SGLT2i are notable

amongst anti-diabetic drugs, since many hypoglycemic agents are associated with weight gain and a higher risk of cardio-renal disorders [74].

5.4. Prevention of oxidative damage

Oxidative stress is closely linked to the pathophysiology of CKDs and DN [19]. Oxidative stress develops when the production of free radical species is increased above physiological levels and overcomes the capacity of the anti-oxidant defense system [75]. As a result, the excess free radicals cause damage to various biological elements [19,75]. Previously, we suggested that oxidative stress induces renal failure by at least nine pathological molecular pathways including modulation of transcription factors, induction of inflammatory responses, enhancement of advanced glycation end product (AGE) and receptor for advanced glycation end product (RAGE) production, up-regulation of protein kinase C (PKC), activation of various molecular mechanisms (such as the hexosamine pathway, the polyol pathway, the autonomic nerve system and the RAS) and, finally, via direct damage to intracellular molecules [19].

SGLT2 inhibition exhibits potent anti-oxidative properties [12,76]. We illustrated previously that SGLT2 inhibitors can prevent oxidative damage via reduction of free radical generation by several pathways [12]. Reported evidence has confirmed that SGLT2is can suppress oxidative stress in various tissues, including the kidneys [77]. Tang et al in 2017 showed that dapagliflozin slows DN progression by down-regulation of free radical progenitors such as Nox4 (nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) 4, Nox2, and the p47phox subunit of Nox4, and urinary excretion of TBARS (Thiobarbituric acid reactive substances, a marker of lipid peroxidation) [77]. Tanaka et al in 2018 reported that treatment with ipragliflozin normalized glucose metabolism and re-adjusted the oxidative balance in kidneys of diabetic animals [78]. Osorio et al in 2012 found that SGLT2 inhibition using phlorizin prevented oxidative stress by promotion of catalase (CAT) and glutathione peroxidase (GPX) activity and reduced nitrogen free radicals in diabetic rats [79]. Ojima et al. in 2015 revealed that empagliflozin may, at least in part, inhibit oxidative stress in DN *via* suppression of the AGE-RAGE axis [80]. It has also been shown that empagliflozin reduces oxidative stress through induction of Nrf2 translocation to the nucleus and activation of Nrf2/ARE signaling in T2D model [81]. In conclusion, the antioxidative properties are another beneficial effect of SGLT2 inhibition for prevention of CKD development [82,83].

5.5. Inhibition of inflammatory responses and fibrotic processes

Inflammatory responses and fibrotic processes are observed in most cases of CKD [77,84]. Progression of CKD is accompanied by higher circulating levels of inflammatory mediators (together with their increased expression and release) and increasing fibrosis [9,83–85]. Recent evidence suggests inflammatory mediators as new therapeutic targets for improvement of renal function in the setting of diabetes [86–88]. Many inflammatory cytokines, including IL (interleukin)-1, IL-6, IL-18, TNF-α, ICAM (intracellular cell adhesion molecules), VCAM (vascular cell adhesion molecules), and MCP-1 (monocyte chemoattractant protein-1), are involved in different aspects of renal injury and are upregulated during uncontrolled hyperglycemia [7,86,89,90]. Moreover, some evidence has shown that increasing levels of inflammatory cytokines, such as IL-18, is closely linked to progression of albuminuria [91]. Inflammatory responses and fibrotic processes in renal proximal tubules are associated with higher TGF-β cytokine expression [73]. Liu et al in 2010 showed that proximal tubular cells cultured in hyperglycemic conditions are accompanied by increased inflammatory and profibrotic mediators [92]. Overall, the inflammatory hypothesis suggests that inflammatory mediators induce renal tissue injuries, such as tubular apoptosis and interstitial fibrosis, either directly or indirectly (via induction of other pathologic pathways such as apoptosis) [7].

SGLT2i have anti-inflammatory effects by reducing serum leptin and IL-6 levels and increasing adiponectin concentrations resulting in improved adipose tissue function [44]{Yaribeygi, 2018 #11;Garvey WT, 2018 #21}. Besides, these antidiabetic drugs mitigate systemic inflammation through decreasing high-sensitivity C-reactive protein concentrations and ameliorating insulin resistance [43]. Also, SGLT2is exert an inhibitory effect on the secretion of IL-1β by macrophages *via* the ROS-NLRP3-caspase-1 pathway [45]. These effects seem to be independent to glucose-lowering effects of SGLT2i. In a previous review of experimental and clinical trial studies, we reported that SGLT2 inhibition, in the setting of diabetes, reduces inflammation via at least five separate molecular pathways; namely, these include modulation of the RAS activity, prevention of hemodynamic variations, reduction of obesity–induced inflammation, alteration of the immune system and readjustment of the redox state towards the normal condition [12]. SGLT2 inhibition may also improve adipose tissue function and regulate serum levels of leptin and adiponectins, leading to reduced tissue inflammation [93]. It has suggested that SGLT2is ameliorate systemic low grade inflammation as well as local tissue inflammation [93].

Panchapakesan et al in 2013 demonstrated that treatment by empagliflozin in human proximal tubular cells caused a reduction in hyperglycemia-dependent TLR (Toll-like receptor) 2 and 4 and NF-κb expression, leading to a reduction in inflammation and fibrosis [94]. Terami et al in 2014 found that dapagliflozin treatment in diabetic animals reduced MCP-1, ICAM-1 and TGF-β, leading to a reduction in inflammation and the fibrotic process in a dose-dependent manner [95]. Vallon et al. in 2013 reported that empagliflozin attenuated diabetes-induced renal injuries by amelioration of inflammation and fibrosis, probably secondary to lowering glucose levels [96]. Thus, prevention of inflammation and fibrotic events are other beneficial renoprotective effects of SGLT2i [96].

5.6. Reduction in plasma uric acid levels

It has been proposed that high plasma levels of uric acid (PUA) might be a risk factor and/or predictor for renal insufficiency [97]; however, this hypothesis is still debatable. An elevated level of PUA independently predicts the development of CKDs and is associated with the progression towards renal failure [97]. Therefore, some therapeutic strategies in CKDs are based upon lowering circulating levels of PUA and inducing its urinary excretion [97]. SGLT2is markedly reduce PUA by stimulation of its excretion in urine [98]. SGLT2is ameliorate PUA via altering tubular transport of uric acid and/or inhibition of GLUT9 (glucose transporter 9, also known as SLC2A9 [Solute carrier family 2, facilitated glucose transporter member 9]) located at the apical membrane of collecting ducts [98,99]. These beneficial effects of SGLT2i are related to glycosuria and, so, these agents increase uric acid excretion in a dose-dependent manner [98,100].

Davies et al in 2015 found that SGLT2 inhibition by canagliflozin attenuated PUA in T2D [101]. Zhao et al in 2018 reported that dapagliflozin decreased PUA in a dose-dependent manner [100]. Xin et al in 2018 confirmed that SGLT2 inhibition by canagliflozin, dapagliflozin or empagliflozin is associated with higher uric acid urinary excretion [102]. Further evidence supports the concept that SGLT2i agents have renoprotective outcomes via lowering PUA [103–105].

5.7. Possible reduction of RAS activation

Hyperactivation of RAS is associated with hemodynamic variations and is present in most types of CKDs [106]. In many cases of renal insufficiency, there is a high level of RAS activity and, therefore, many therapeutic protocols have focused upon the modulation of RAS activation as a main target [106–108]. Activation of RAS is associated with such pathophysiological outcomes in kidneys as fibrosis, BP elevation

Table 2
The major clinical studies addressing the renoprotective effects of SGLT2 inhibitors.

Clinical Trials	Used Drug(s)	Total Population	Outcome of SGLT2i Therapy	Ref.
EMPA-REG OUTCOME trial (NCT01131676)	Empagliflozin	7020	Lower rate of cardiovascular death or hospitalization	[132]
EMPA-REG OUTCOME trial (NCT01131676)	Empagliflozin	7020	Slows progression of kidney disease	[130]
CANVAS-R (NCT01989754)	Canagliflozin	10,142	Lower risk of cardiovascular events, reduction in albuminuria and eGFR, and death from renal causes	[128,129]
–	Dapagliflozin	282	Reduction in glycaemic parameters and body weight	[133]
–	Canagliflozin	2313	Reduction in serum uric acid levels	[101]
–	Canagliflozin	1450	Slows the progression of CKD, reduces albuminuria and eGFR	[134]
–	Dapagliflozin	62	Improvement of UACR, uNAG, and kidney morphology, reduction in body fat mass	[135]
ClinicalTrials.gov (NCT00680745)	Dapagliflozin	597	Improved glycemic control and reduced body weight	[136]
DECLARE (NCT01730534)	Dapagliflozin	17160	Lower rate of cardiovascular death or hospitalization	[137]
CREDENCE (NCT02065791)	Canagliflozin	4401	Lower rate of end-stage kidney disease or renal or cardiovascular death	[42]
VERTIS (NCT01986881)	Ertugliflozin	About of 8000	In progress	–
EMPA-KIDNEY (NCT03594110)	Empagliflozin	5000	In progress	–
Dapa-CKD (NCT03036150)	Dapagliflozin	4000	In progress	–

(CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; UACR = urinary albumin/creatinine ratio; uNAG = urine N-acetyl-β-glucosaminidase).

and apoptosis and therefore RAS blocking agents are now considered as a central pillar of CKD prevention/treatment [109]. It has been suggested that SGLT2 inhibition may modulate RAS activity [106]. Shin et al in 2016 demonstrated that SGLT2i ameliorates intrarenal and systemic RAS activity [106]. However, this finding is inconsistent with previous studies. In this regard, Yoshimoto et al in 2017 reported that SGLT2i therapy in T2D patients is not accompanied by RAS activation [110]. Also, Li et al in 2018 demonstrated that daily treatment with a selective SGLT2 inhibitor of TA-1887 for 10 weeks did not activate either systemic or intrarenal RAS in dysfunctional kidneys [111]. Thus, although SGLT2i therapy alters renal tubular Na^+ handling, it does not induce RAS activation [110]. However, there are a few reports suggesting that SGLT2 inhibition increases RAS mediators such as renin, angiotensin II and aldosterone, probably secondary to volume depletion and activation of compensative mechanisms [112,113]. Hence, the possible effect of SGLT2 inhibitors on RAS activation is uncertain and requires further investigation.

5.8. Reduction in natriuretic peptides level

Atrial natriuretic peptide (ANP) is a biologic protein with hormonal properties that is released by the cardiac atria and induces volume reduction by a urinary natriuresis process; it, therefore, plays an important role in cardio-renal homeostasis as well as in vascular physiology [114–116]. Although some clinical trials have suggested that low dose ANP infusion protects against renal dysfunction [117], several *in vitro* and *in vivo* studies have demonstrated that elevation of ANP plasma levels are a marker of renal dysfunction as occurs in CKDs [118–120]. Ogawa et al in 2015 reported that the age-dependent increase in ANP levels is closely correlated to CKD development in Japanese patients with progressive renal dysfunction [118]. In addition, other types of natriuretic peptides, such as brain derived peptides (BNP), may be involved in the progression of CKDs [121].

SGLT2 inhibition lowers the ANP plasma level [122]. Wang et al in 2016 found that SGLT2 inhibitors ameliorated ANP secretion in newly diagnosed T2D patients [122]. Januzzi et al in 2017 reported that SGLT2i by canagliflozin delayed the elevation of BNP in older patients with T2D [123]. Moreover, Yanai et al in 2018 established that SGLT2 inhibition improved renal function via a reduction in brain-derived natriuretic peptide [121]. However, the reported beneficial role of low dose administration of natriuretic peptides [117] is unclear and premature in terms of renal function and requires further investigation.

5.9. Other possible mechanisms

There are other suggested pathways that may be involved in the renoprotective effects of SGLT2is, such as inhibition of sympathetic hyperactivation [124], increase in glucagon release [125], alteration of mitochondrial morphology [126], elevation of hematocrit [127], improvement of tubulointerstitial hypoxia [127], and albuminuria-lowering effect [42]. However, these mechanisms are still uncertain and further evaluation is needed.

6. Clinical trials

Beyond experimental data, we have also strong clinical evidences indicating the renoprotective roles of SGLT2i in diabetic and non-diabetic patients (Table 2). Large clinical trials as, CANVAS, EMPA-REG, DELIGHT, and CREDENCE, have emphasized the potent renoprotective effects of SGLT2is via aforementioned molecular mechanisms in patients with kidney failure [42,68,128–131]. Recently, CREDENCE trial reported that SGLT2i decreases the risk of dialysis, transplantation, or a sustained reduction in the eGFR in patients with type 2 diabetes and nephropathy (eGFR of $30 < 90$ ml/min/1.73 m^2) (Perkovic 2019). CANVAS study found a beneficial effect of SGLT2i with respect to the progression of albuminuria and the composite outcome of a sustained reduction in the eGFR, the need for renal-replacement therapy, or death from renal causes in patients with type 2 diabetes [128]. Furthermore, CANVAS Program, in a prespecified exploratory analysis, supported the renoprotective effect of SGLT2i by decreasing the risk of sustained loss of kidney function, attenuated eGFR delcline, and reduction in albuminuria in patients with type 2 diabetes [129]. EMPA-REG OUTCOME trial SGLT2i showed a significant risk reduction of incident or worsening nephropathy, progression to macroalbuminuria, and the initiation of renal-replacement therapy in patients with type 2 diabetes and an eGFR of at least 30 ml/min/1.73 m^2 [69]. Also, DELIGHT study revealed that SGLT2i slows the progression of kidney disease through the albuminuria-lowering effect in patients with type 2 diabetes and moderate-to-severe chronic kidney disease [131]. Thus, these clinical trials have clearly confirmed the previous experimental evidences and demonstrated that SGLT2 inhibition by commonly used drugs markedly improve renal function via several molecular pathways such as readjustment in glycemic profile; which in turn prevent of further pathophysiologic mechanisms as oxidative damages, inflammation, apoptotic and fibrotic processes; in patients with dysfunctional kidneys. Also, these clinical evidences have shown other renoprotective effects of SGLT2i by lowering the body weight, reduction in albuminuria, regulating urinary albumin/creatinine ratio and improvement in renal cells' morphology and lower histological damages leading to improved eGFR in evaluated populations. It is important to note that SGLT2i have the potential to induce renal protection by lowering intraglomerular pressure and glomerular hyperfiltration beyond glucose control. However, more clinical investigations are still needed to fully understanding the renoprotecting outcomes of these drugs in humans along with

recognizing the exact involved molecular mechanisms as previously suggested by experimental studies. In Table 2, we present the major clinical studies reporting the renoprotective effects of SGLT2i.

7. Conclusion

Diabetes-induced kidney disease is the major precipitating cause of renal replacement therapy worldwide. Therefore, protection of the kidneys in diabetic patients is critically important. Beyond the hypoglycemic effects, SGLT2 inhibition has renoprotective properties. SGLT2is may protect against renal failure via at least eight molecular mechanisms, being the effects on hyperglycemia and hypertension the most important, owing to the key role of these conditions in the pathogenesis of DN. The knowledge relative to the mechanisms implicated in the SGLT2i off-targets effects is progressively increasing, thus explaining the benefits reported by the large clinical trials for this class of hypoglycemic drugs.

Declaration of Competing Interest

Dr. Banach has served on speaker's bureau and as an advisory board member for Amgen, Sanofi-Aventis and Lilly.

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