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SGLT2 inhibition and kidney protection

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Abstract

Type 2 diabetes mellitus (T2DM) is a growing public health concern worldwide. Numerous drug classes are available for treatment, however, their efficacy with regard to diabetes-induced renal and cardiovascular (CV) complications remains limited. Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) are a new class of blood glucose lowering medications that block renal glucose reabsorption and have protective effects on the kidney and the heart. This review focusses on the effects of SGLT2 inhibitors on the kidney and renal outcome: it briefly outlines renal glucose handling in diabetes and its role in glomerular hyperfiltration and renal hypoxia; describes how SGLT2 inhibitors induce an early, reversible reduction in glomerular filtration rate (GFR) and preserve GFR in the long-term in patients with T2DM; discusses whether the enhanced active transport in the renal outer medulla (OM) in response to SGLT2 inhibition is friend or foe; proposes how the blood pressure lowering and heart failure protective effect of SGLT2 inhibitors can be preserved in chronic kidney disease (CKD) despite attenuated antihyperglycemic effects; and examines whether SGLT2 inhibition enhances the incidence or severity of acute kidney injury (AKI).

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health concern [1]. The main feature of T2DM is chronic or periodic hyperglycemia which in turn can lead to progression of the underlying metabolic disease and impair organ functions including cardiovascular (CV) and renal complications. Therefore, lowering blood glucose levels (HbA_{1c} < 7%) is the primary therapeutic strategy to slow the progression of DM and prevent or delay subsequent damage. Multiple drug classes are available for treatment of T2DM (including insulin, metformin, sulphonylureas, glitazones, and others), however significant drawbacks include limited effectiveness with regard to improving CV outcome and some may even worsen CV

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Disclosure

Over the past 36 months, V.V. has served as a consultant and received honoraria from Bayer, Boehringer Ingelheim, Intarcia Therapeutics, Astra-Zeneca, Janssen Pharmaceutical, Eli Lilly, and Merck.

Competing interests

The authors declare that there are no competing interests associated with the manuscript.

mortality. For example, the safety in heart failure is equivocal for sulphonylureas and insulin, and thiazolidinediones are contraindicated in patients with or at the risk of heart failure [2].

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2) constitute a new class of blood glucose lowering drugs that has been approved for the treatment of T2DM. On the whole kidney level and in nor-moglycemia, SGLT2 is responsible for the reabsorption of ~97% of the filtered glucose. The drugs directly block SGLT2 and thereby inhibit renal glucose reabsorption, increase urinary glucose excretion, and effectively lower hyperglycemia. The approach of SGLT2 inhibition differs from many other antidiabetic therapies by its insulin-independent mode of action, which makes the drugs effective at all stages of T2DM. Moreover, SGLT2 inhibitors are associated with a low risk of hypoglycemia, and in addition can lower body weight, blood pressure, and serum urate levels, which all contribute to an attractive clinical drug profile [3–5]. Possibly as a consequence of these pleiotropic effects, clinical trials conducted in T2DM patients with high CV risks have shown that SGLT2 inhibitors can reduce relevant CV and renal adverse outcomes [6–8].

Here we aim to discuss the beneficial effects of SGLT2 inhibition on renal function and kidney integrity that may explain the improvement in renal outcome observed in the recent large clinical trials. The bi-phasic effect of SGLT2 inhibitors on glomerular filtration rate (GFR) are outlined, including an initial reduction in GFR followed by a sustained preservation. We also discuss mechanisms that can put stress on the kidney but may ultimately contribute to beneficial effects of SGLT2 inhibitors on the kidney and in patients with heart failure. Finally, we ask whether SGLT2 inhibitors enhance the risk of acute kidney injury (AKI). This review summarizes evidence from clinical trials as well as recent concepts emerging from mathematical modeling studies and basic research studies.

Renal glucose reabsorption in normoglycemia

In normoglycemia and with a normal GFR, the two kidneys in an adult individual filter up to ~ 180 g of glucose per day, which equals ~30% of the daily energy expenditure. Filtered glucose is nearly completely reabsorbed in the proximal tubules (PT) through the co-ordinated action of several apical and basolateral epithelial transporters [9]. SGLT2 and SGLT1 are secondary active symporters that are expressed in the apical brush border of the PT. They reabsorb glucose together with Na^+ following an electrochemical gradient for Na^+, which is established by the basolateral Na^+/K^+-ATPase. Studies in gene-targeted mice indicated that SGLT2 reabsorbs all filtered glucose in the early PT (S1/S2 segments) and the majority of glucose or ~97% on the whole kidney level in normoglycemia; in comparison, SGLT1 is responsible for the reabsorption of the remaining glucose in the late PT (S2/S3 segments) [10–12]. Driven by the glucose concentration gradient between the cytosol and peritubular interstitium, facilitative glucose transporters GLUT2 and GLUT1 in the basolateral membrane allow glucose to exit from the PT cells. Glucose enters the peritubular capillaries by convection and is delivered as energy substrate to more distal tubules, which in contrast with the early PT can metabolize glucose or glucose is returned to the systemic blood stream. Thus, renal glucose reabsorption is an important physiological process, which, by retaining glucose, prevents substantial energy substrate loss into the urine and contributes

to the intrarenal and systemic metabolic control. Ultimately, the glucose returning to the systemic circulation helps to maintain blood glucose levels.

Renal glucose handling in diabetes and its role in glomerular hyperfiltration and renal hypoxia

Diabetes is characterized by hyperglycemia, which enhances the filtered glucose load to the PTs. A typical feature in the early stages of diabetes is tubular growth, characterized by an early phase of hyperplasia followed by hypertrophy particularly of the PT [13]. PT growth is accompanied by increased glucose reabsorption capacity and can be associated with higher renal protein expression of SGLT2 [14,15]. These adaptations allow greater tubular glucose reabsorption, such that more filtered glucose can be returned to the bloodstream. As a consequence, enhanced glucose reabsorption via SGLT2 helps to maintain hyperglycemia, which may be considered maladaptive.

SGLT2- and SGLT1-mediated glucose reabsorption is associated with Na^+ reabsorption. Therefore, diabetes-induced tubular growth and increased expression of SGLT2 not only increase glucose reabsorption but also enhance proximal tubular Na^+ and fluid reabsorption [16–18]. This reduces the fluid delivery and the concentrations of Na^+, Cl^-, K^+ in the tubular fluid at the end of the thick ascending limb, where a couple of specialized tubular cells form the macula densa [18]. The lower Na^+, Cl^-, K^+ concentrations are sensed by the macula densa cells and cause the single nephron GFR (SNGFR) to increase via the mechanism of tubuloglomerular feedback (TGF) [18]. The role of the TGF is to stabilize the salt and fluid delivery to the further distal nephron, where the fine regulation of salt and fluid balance is established. In addition, the reduced fluid delivery to the distal tubule lowers the tubular back pressure in Bowman space [18], which increases the effective glomerular filtration pressure and may explain up to 50% of diabetic hyperfiltration [19]. Thus, a primary increase in tubular reabsorption, in part mediated by SGLT2, contributes to the early hyperfiltration in the diabetic kidney [5].

A sustained glomerular hyperfiltration has been proposed to participate in the development and progression of diabetic kidney disease [13,20–22]. Hyperfiltration increases tubular transport load and transport work since basically all the salt and fluid that is filtered by the kidneys need to be reabsorbed by the tubular system. The increase in active tubular transport work enhances oxygen consumption. Using mathematical modeling of the rat nephron, diabetes was predicted to increase Na^+ transport and Na^+ transport-dependent oxygen consumption (active Q_{O2}) by ~50 and 100%, respectively [23]. Moreover, in a rat model of type 1 diabetes mellitus (T1DM), a significant decrease in oxygen tension (P_{O2}) was detected in the renal cortex [24], i.e. the region where the PT segments are located that actively reabsorb most of the glomerular filtrate and are expected to show the largest increases in tubular active Q_{O2} when GFR increases [23,25]. Hypoxia is an important factor in the development of renal interstitial fibrosis and a major pathway in the progression to chronic kidney disease (CKD) [26,27]. Moreover, preserving renal oxygenation particularly in the kidney cortex has been proposed to preserve kidney function in patients with CKD [28]. Thus, GFR is often increased in the early diabetic kidney and has been proposed as a

risk factor for diabetic kidney disease [22]. As discussed below, inhibition of SGLT2 can lower hyperfiltration and induce distinct effects on renal oxygenation.

SGLT2 inhibitors and their effects on cardiac and renal outcome in type 2 diabetes

SGLT2 mediates most of renal glucose reabsorption in normoglycemia and its contribution is further enhanced in diabetes, thereby contributing to the maintenance of hyperglycemia. As a consequence, SGLT2 inhibitors were developed to reduce glucose reabsorption in the early PT, thereby increasing urinary glucose excretion and lowering hyperglycemia. Four SGLT2 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for use in patients with T2DM: empagliflozin (Jardiance), dapagliflozin (Farxiga), canagliflozin (Invokana), and ertugliflozin (Steglatro). According to a meta-analysis of patients with type 2 diabetes, SGLT2 inhibitors decreased HbA1C levels by 0.5–0.7% at 12 weeks of treatment and this effect persisted for at least up to 52 weeks [29].

As part of post-marketing and drug efficacy and safety studies for new antidiabetic drugs, large clinical outcome trials have also been conducted for SGLT2 inhibitors. So far, two SGLT2 inhibitors have been evaluated: empagliflozin in the EMPA-REG OUTCOME trial [7,8] and canagliflozin in the CANVAS Program [6]. The EMPA-REG OUTCOME trial assessed the effect of empagliflozin compared with placebo on CV outcomes in T2DM patient with high CV risk and an estimated GFR (eGFR) 30 ml/min/1.73 m^2 over a period of 192 weeks, with a secondary analysis of renal adverse outcomes [7,8]. Approximately 80% of the patients were taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers at baseline as part of standard of care. Empagliflozin improved renal outcomes defined by reduced risk of incidents or worsening nephropathy, reduced progression to macroalbuminuria, reduced incidence of renal-replacement therapies and reduced occurrence of doubling of serum creatinine, compared with placebo. The results for the composite renal outcomes were validated in a post hoc sensitivity analysis and in a subgroup analysis of patients with prevalent kidney disease defined as eGFR (MDRD) *60* ml/min/1.73 m^2 and/or macroalbuminuria (urine albumin-to-creatinine ratio > 300 mg/g) at baseline [7]. More recently, the CANVAS Program reported similar renal protective effects of canagliflozin in T2DM patients [6]. The CANVAS Program integrated data from two clinical trials carried out on T2DM patients with high CV risk and an eGFR 30 ml/min/1.73 m^2 over a median period of 188 weeks. Canagliflozin reduced the occurrence of progression to albuminuria and increased the occurrence of regression of albuminuria. This was associated with less frequent sustained 40% decrease in eGFR, less frequent need for renal-replacement therapy and less frequent deaths from renal causes [6]. In addition to these beneficial effects on the kidney, both trials also went beyond the requisite CV safety parameters to show ~35% reductions in the incidence of heart failure [6,8]. Thus, SGLT2 inhibitors can have protective effects on the kidney and lower the incidence of heart failure in patients with T2DM and high CV risk.

SGLT2 inhibitors induce an early, reversible reduction in GFR and can preserve GFR in the long-term in type 2 diabetic patients

The EMPA-REG OUTCOME trial determined eGFR at several time points over the treatment period as well as during a follow-up after discontinuation of treatment. Empagliflozin induced an initial decrease in eGFR (measured at week 4 of treatment) whereas placebo showed no significant effect at this time point. During the subsequent long-term follow-up until week 192, eGFR remained stable in SGLT2 inhibitor-treated participants while placebo treatment was accompanied with a progressive decrease in eGFR: the adjusted estimates of annual decreases in eGFR were 0.19 $^{+}$ 0.11 ml/min/1.73 m^2 in the empagliflozin group, as compared with a significantly greater decrease in 1.67 $^{+}$ 0.13 ml/min/1.73 m^2 in the placebo group. Most importantly, after treatment discontinuation, eGFR increased to baseline in the empagliflozin group while eGFR remained unchanged at reduced levels in the placebo group [7]. Although no statistical analysis or commentary was provided by the authors, a closer look at the EMPA-REG OUTCOME data provided a hint that the reduction in eGFR in response to the SGLT2 inhibitor after the initial drop remained sustained when baseline eGFR was >60 ml/min/1.73 m^2, while the profile in patients with baseline eGFR >60 ml/min/1.73 m^2 appeared to show only a transient reduction in eGFR followed by a slow recovery to baseline over time despite continuous treatment [7].

A similar detailed temporal analysis of eGFR changes was not specifically reported in the above described CANVAS program outcome study [6]. However, assessments of temporal changes in eGFR were also performed across the studies of the canagliflozin clinical development program in patients with T2DM as reported in a review in 2015 [30]. Across studies, treatment with canagliflozin was generally associated with early reductions in eGFR (of ~4 ml/min/1.73 m^2) accompanied with commensurate increases in serum creatinine and blood urea nitrogen levels compared with placebo [30]. The reduction in eGFR was greatest at the first post-baseline visit (~3–6 weeks) and eGFR subsequently stabilized or recovered over the study period of up to 102 weeks. According to a subgroup analysis in patients with Stage 3A and 3B CKD, a small initial decline in eGFR was seen with canagliflozin, followed by a return toward baseline, consistent with the trend observed across studies and in patients with normal kidney function [30]. Amongst a subset of 396 patients of the canagliflozin phase 3 development program, eGFR was also measured following discontinuation of canagliflozin: eGFR was found to increase toward baseline levels, particularly in the high-dose canagliflozin group (300 mg/day), which had induced a stronger initial eGFR reduction, while eGFR numerically further decreased in the placebo group [30].

The temporal eGFR effect of dapagliflozin has also been evaluated in several clinical studies in T2DM patients. Kohan et al. [31] analyzed 12 placebo-controlled, randomized clinical trials in T2DM patients with normal or mildly impaired renal function (eGFR >60 ml/min/1.73 m^2). The authors observed that dapagliflozin induced a reduction in eGFR after 1 week compared with placebo, and eGFR subsequently increased to near baseline values after 24 weeks and remained stable until the end of the treatment at 102 weeks. At that time GFR was not significantly different from placebo control [31]. The effect of the SGLT2 inhibitor

empagliflozin on GFR (by inulin clearance) was also determined in type 1 diabetic patients: empagliflozin induced a significant reduction in GFR in patients with glomerular hyperfiltration at baseline when measured after 8 weeks of treatment [32].

Together these clinical studies indicated that SGLT2 inhibitors often induce an initial decrease in eGFR in patients with T2DM and eGFR at baseline > 30 ml/min/1.73 m^2. Subsequently, eGFR remains stable over time and after drug discontinuation it is restored to baseline, or eGFR already returns toward baseline during continuous SGLT2 inhibition. Data with empagliflozin suggest that the latter profile may particularly apply to patients with lower baseline eGFR. Overall, the data indicate that the initial eGFR reduction in response to SGLT2 inhibition is reversible, and thus seems to reflect functional rather than structural changes. In the long-term, SGLT2 inhibition has the potential to preserve eGFR/renal function in T2DM patients with high CV risk when compared with placebo treatment, as indicated by the renal outcome data of the EMPA-REG OUTCOME and the CANVAS program [6,7].

How can SGLT2 inhibition acutely lower GFR and preserve GFR in long term?

The acute GFR lowering effect of SGLT2 inhibition relates to the contribution of SGLT2 to the primary tubular hyper-reabsorption in the diabetic kidney that secondarily causes glomerular hyperfiltration [5], as discussed above. Thus, inhibition of SGLT2 attenuates the diabetes-induced hyperreabsorption of glucose and sodium in the early PT. Recent studies indicated that inhibition of SGLT2 may also negatively affect early proximal tubular Na^+ reabsorption via the Na^+-H^+-exchanger NHE3 [5]. Together these effects increase sodium and chloride delivery to the downstream macula densa [18,33], which through the TGF mechanism enhances the tone of the afferent arteriole and consequently lowers GFR by reducing glomerular plasma flow and/or intraglomerular pressure (Figure 1(1)). Through the osmotic effect of non-reabsorbed glucose, SGLT2 inhibition enhances the fluid delivery to the distal tubule, which increases the tubular back pressure, i.e. the hydrostatic pressure in Bowman’s space, which through the reduction in effective filtration pressure also lowers GFR (Figure 1(2)) [18]. Partial or more complete return of eGFR after the initial dip in response to sustained SGLT2 inhibition, as seen in some clinical studies (see above), may in part relate to compensatory up-regulation of NaCl reabsorption in the loop of Henle as suggested by rodent studies [33].

For the past 30 years, the most effective treatment for slowing the progression of diabetic glomerulopathy has remained blockade of the renin-angiotensin system, which similarly works through a hemodynamic mechanism [34]. It might be more than coincidence that the time course of eGFR decline after SGLT2 blockade is similar to that of angiotensin blockade, which also causes an immediate functional decline in GFR but slows disease progression to a point at which eGFR becomes higher in treated patients than in non-treated patients. In other words, one may speculate that the initial and functional decrease in eGFR in response to blockade of angiotensin or SGLT2 may help to preserve kidney function in the long term.

To the extent that the physical and metabolic burden of hyperfiltration induces renal damage in the diabetic environment, SGLT2 inhibitors should be renoprotective. Mathematical modeling predicted that the reduction in GFR in the diabetic kidney by SGLT2 inhibition reduces tubular transport work (Figure 1(3)) and thus oxygen requirement (Figure 1(4)), particularly in the proximal convoluted tubule and thus in the kidney cortex [23,25]. This is consistent with studies in diabetic rats in which the dual SGLT2/SGLT1 inhibitor phlorizin acutely enhanced P_{O2} in the kidney cortex [24] (Figure 1(5)). Reducing GFR and thus the tubular load may also attenuate diabetic tubular growth (Figure 1(6)) [13]. A decrease in GFR can reduce the filtered amount of albumin, which lowers albuminuria in accordance with clinical trials, but also reduces the burden of PTs to reabsorb albumin. The reduced exposure of the tubular system to albumin and other proteins and substances has the potential to attenuate tubulointerstitial inflammation and in the long-term preserve kidney integrity (Figure 1(6)) [27]. SGLT2 inhibition also lowers tubular transport work by lowering blood glucose levels and in the early PT also by directly inhibiting Na^+-glucose cotransport (Figure 1(7)). Lowering blood glucose without inducing hypoglycemia is also expected to protect glomerular and renal tubular and vascular integrity (Figure 1(7,8)) [27,35]. SGLT2 inhibitors do not increase the hypoglycemia risk due the intact metabolic counter regulation, including up-regulation of hepatic gluconeogenesis [36,37]. Moreover, SGLT1 in the downstream late PT has a significant transport capacity [11], which eliminates glucose excretion during SGLT2 inhibition when the filtered glucose falls below the transport capacity of SGLT1 (~80 g/day). This is relevant since episodes of hypoglycemia can impair cardioprotective effects [38]. The metabolic counter regulation in response to SGLT2 inhibition can also include a modest ketosis. The blood glucose lowering effect of SGLT2 inhibition increases glucagon levels and reduces endogenous insulin levels or insulin dosage, which in turn increases lipolysis and hepatic ketone body production and release [39]. The resulting increase in ketone bodies may serve as a preferred energy source in the kidney and the heart [40].

SGLT2 inhibition enhances active transport in the renal outer medulla – friend or foe?

SGLT2 inhibition is shifting tubular glucose load and transport work downstream to segments in the outer medulla (OM), including the S3 segment of the PT, where SGLT1 partially compensates for SGLT2 blockade, as well as the medullary thick ascending limb of the loop of Henle (mTAL). The computational model of a rat nephron in diabetes predicted that chronic SGLT2 inhibition increases active Q_{O2} by 26% in the S3 segment and by 2% in the mTAL [23] (Figure 1(10)). Outer medullary P_{O2} is low under physiological conditions due to low perfusion and oxygen shunting, and is further reduced in diabetes and by SGLT2 inhibition. These computational predictions are consistent with data in a T1DM rat model, where diabetes reduced P_{O2} in kidney cortex and medulla. Moreover, application of phlorizin, which can inhibit both SGLT2 and SGLT1 but inhibits the former at ten times lower concentrations, enhanced cortical P_{O2} (see above) but reduced medullary P_{O2} in both T1DM and control rats [24], consistent with the proposed shift of active transport to downstream nephron segments in response to SGLT2 inhibition (Figure 1(10)) [23,25]. The modeling studies proposed that the reduction in GFR in response to SGLT2 inhibition

played a prominent role for the increase in cortical P_{O2} and attenuated the reduction in medullary P_{O2} [23].

By lowering medullary P_{O2}, SGLT2 inhibition may make the outer medullary region more vulnerable to hypoxia and injury (Figure 1(5*)). On the other hand, the former may induce hypoxia-inducible factor HIF-1 and HIF-2 signaling pathways in the deep cortex/OM and enhance the expression of protective genes (Figure 1(11)). SGLT2 knockout increased renal mRNA expression of hemoxygenase-1 [14], an HIF-1-α induced, tissue protective gene. HIF-2 activation in fibroblast-like interstitial cells may enhance erythropoietin (EPO) expression, which could increase hematocrit (Figure 1(12)) and thereby improve the oxygen transport capacity of the blood and thereby renal cortical and medullary oxygen delivery (Figure 1(13)) but also facilitate oxygen delivery to the heart and other organs (Figure 1(14)) [41,42]. This hypothesis is supported by clinical data showing that treatment with the SGLT2 inhibitors empagliflozin and dapagliflozin was associated with a rapid increase in hematocrit, which, besides a potential medullary hypoxia signal, is likely due to the diuretic and natriuretic effects and the associated volume loss (Figure 1(15)) [43]. In this regard, changes in hematocrit and hemoglobin from baseline explained 51.8 and 48.9%, respectively, of the effect of the SGLT2 inhibitor empagliflozin compared with placebo on the risk of CV death [44]. Thus, SGLT2 inhibition may act as a double-edge sword regarding its consequences on medullary oxygenation and further studies are needed to better understand this issue. Along these lines, sustained activation of the HIF-1 or HIF-2 pathway in the rodent kidney has been linked to the development of interstitial fibrosis [45–47], but the clinical relevance of these observations remains unclear.

How is the blood pressure lowering and heart failure protective effect of SGLT2 inhibitors preserved in CKD despite attenuated antihyperglycemic effects?

The amount of filtered glucose determines the glycosuric and blood glucose lowering effect of SGLT2 inhibition. As a consequence, the antihyperglycemic effects of SGLT2 inhibitors are attenuated in patients with reduced GFR. In contrast, the blood pressure lowering and heart failure protective effects are preserved in patients with CKD and reduced GFR (eGFR ≥30 ml/min/1.73 m^2) [48,49]. Modeling studies of CKD and nephron loss predicted that SGLT2 inhibition in remaining nephrons with increased SNGFR markedly decreases net PT Na^+ reabsorption and induces a natriuretic and diuretic effect [42]. This was in large part due to the resulting high glucose load on the single nephron level, which osmotically binds water, lowers luminal Na^+ concentrations, and secondarily increases paracellular Na^+ secretion in PTs. In other words, the model predicted that the chronic natriuretic and diuretic effects of SGLT2 inhibition persist in diabetic patients with CKD or reduced total GFR. The preserved increase in fluid and Na^+ load to the distal tubule also preserved the kaliuretic effect of chronic SGLT2 inhibition; this may reduce K^+ retention in diabetic patients with CKD and enhance the tolerability of blockers of the renin-angiotensin-aldosterone system and thus allow their continued use, which is expected to be of therapeutic benefit [42]. The modeling approach also predicted that the SGLT2 inhibition-induced changes in the oxygen signal at the outer medullary sensor, as discussed above, are likewise preserved in CKD [42].

Finally, the model predicted that hyperglycemia facilitates the diuretic and natriuretic potential of SGLT2 inhibition, also in CKD [42]. This may explain why effects of SGLT2 inhibitors on volume status rather than HbA1c levels were the most important mediators reducing the risk of CV death [44]. Thus, the attenuated blood glucose lowering effect of SGLT2 inhibitors in CKD may not be all disadvantageous [42].

Does SGLT2 inhibition enhance the incidence or severity of AKI?

Despite the described potential beneficial long-term effects of a modest, sustained, and functional GFR reduction induced by SGLT2 inhibition, the concern has been raised that the initial decrease in GFR at the onset of treatment may increase the risk of AKI, especially in patients with increased susceptibility, including pre-existing low kidney function. In 2016, the U.S. FDA Adverse Event Reporting System (FAERS) reported 101 cases of AKI in canagliflozin and dapagliflozin-treated T2DM patients, with half of the cases occurring within 1 month or less after beginning of the treatment, i.e. at the onset of treatment [50]. At the time of diagnosis, 45% of reported cases were associated with kidney function changes defined by increased serum creatinine (median increase of 1.6 mg/dl, n=32) and reduced eGFR (median decrease of 46 ml/min/1.73 m^2, n=13). Amongst the 101 cases, 83 cases (or 82%) reported concomitant drug use that may predispose to AKI (non-steroidal anti-inflammatory drugs (NSAID), ACE inhibitor, diuretics) and 10 reported history of CKD or previous episodes of AKI. The SGLT2 inhibitor was discontinued in 78 cases and improvement in serum creatinine or eGFR was reported in 56 individuals. However, 11 patients did not recover, including 4 deaths, and 3 others recovered with sequelae. While these observational studies cannot prove a causal relationship, the data raised the possibility that the use of SGLT2 inhibitors in T2DM patients may lead to AKI, the severity of which may vary depending on a patient's medical history and/or on concomitant use of other treatments. Lowering of serum creatinine and increasing eGFR after drug discontinuation is consistent with the reversibility of SGLT2 inhibition and the functional nature of the GFR reduction induced by these drugs, but the data also raise the possibility that under certain conditions kidney injury may occur that is not reversible. The FAERS data indicated the need to study in more detail the question whether the use of SGLT2 inhibitors increases the risk of AKI.

To further address this issue, Nadkarni et al. [51] performed a propensity-matched analysis to evaluate the risk of AKI in large cohorts of T2DM patients in response to the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin compared with non-users (1584 users compared with 1584 non-users) [51]. The study found no increased risk of AKI in T2DM patients receiving a SGLT2 inhibitor compared with non-users over a follow-up period of almost 18 months; the study even observed a trend toward a reduced risk in SGLT2 inhibitor treated patients. Moreover, when AKI occured, the severity was similar in users and matched non-users. Similarly, the CANVAS Program reported that the use of canagliflozin in T2DM patients with high CV risk was not associated with a higher risk of AKI compared with placebo [6]. The EMPA-REG OUTCOME trial found that events that were consistent with acute renal failure, including AKI, and hyperkalemia were reported in a lower percentage of patients in the empagliflozin group than in the placebo group [7]. To identify events suggestive of acute renal failure/AKI in the EMPA-REG OUTCOME trial,

the FDA used and reported a standardized Medical Dictionary for Regulatory Activities (MedDRA) query [52]. The FDA reported that “the overall incidence of these events was slightly higher in the placebo group compared to the empagliflozin group. Serious ‘decreased renal function’ events were also slightly more common in the placebo group. While the incidence of events increased with increasing age and with decreasing eGFR, there was slightly higher in placebo subjects in each of the subgroups.” Further analyses indicated that “in the first 30 days, there were slightly more events in the empagliflozin treated group (0.9% with empagliflozin vs. 0.7% with placebo). Similarly, in the first 90 days there were slightly more events in the empagliflozin treated group (1.5% with empagliflozin vs. 1.2% with placebo).” The authors concluded that ‘the observed incidence in the early period suggested a slightly increased risk of AKI with empagliflozin compared with placebo’ [52]. However, no higher incidence was found in emapgliflozin compared with placebo in the 30 or 90 days results for ‘renal failure’ (placebo compared with empagliflozin: 0.2 compared with 0.2% and 0.3 compared with 0.3%, for 30 and 90 days, respectively), ‘AKI’ (0.1 compared with 0.1% and 0.2 compared with 0.1%), ‘azotemia’ (0.0 compared with 0.0% and 0.0 compared with 0.0%), and ‘acute prerenal failure’ (0.0 compared with 0.0% and 0.0 compared with 0.0%). The difference was solely based on differences in ‘renal impairment’ (0.3 compared with 0.5% and 0.7 compared with 1.0%), which may reflect the expected empagliflozin-induced early lowering in GFR, which increases serum creatinine.

Overall, renal adverse events were also balanced between placebo and dapagliflozin treated groups in a meta-analysis [31]. Moreover, in T2DM patients with moderate kidney function impairment (baseline GFR >30 and *<60* ml/min/1.73 m^2) as well as in patients older than 65 years, renal adverse events were slightly more frequent in dapagliflozin treated individuals compared with placebo. Again, the most common renal event was serum creatinine increase. No events of acute tubular necrosis were reported. The authors concluded that in patients with normal or mildly impaired renal function, dapagliflozin is not associated with increased risk of acute renal toxicity or deterioration of renal function [31]. An ongoing clinical trial is evaluating the risk of AKI in T2DM patients exposed to dapagliflozin compared with other antidiabetic treatments [53]. Another trial is assessing the effects of SGLT2 blockade by canagliflozin compared with placebo over 66 months on renal and CV outcomes in 4401 participants with T2DM and diabetic nephropathy (CREDENCE). The latter study will provide more insights into the effects of SGLT2 inhibition on the progression of renal impairment in patients with established diabetic kidney disease compared with placebo-treated patients [54]. The Renoprotective Effects of Dapagliflozin in Type 2 Diabetes (RED) phase 4 trial is another ongoing study assessing the renoprotective effects of SGLT2 inhibition in T2DM individuals compared with a standard antidiabetic treatment, the sulphonylurea gliclazide. In this study, 44 participants with T2DM are treated with dapagliflozin or gliclazide over 12 weeks. Notably, kidney function and hemodynamics are assessed by GFR and effective renal plasma flow measurements, and tubular function is measured by fractional excretion of several electrolytes and solutes. Moreover, urinary biomarkers of kidney injury neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and urinary albumin excretion are secondary outcomes assessed in the RED trial. Overall, the latter study will expand our knowledge regarding the potential

renoprotective effects of SGLT2 inhibition through renal hemodynamic changes, and more importantly it will compare kidney injury markers between treatment with SGLT2 inhibition and a sulphonylurea [55].

Indeed, the most important question is not whether SGLT2 inhibition modestly enhances serum creatinine, which is expected initially due to the GFR reduction, but whether the treatment enhances markers of kidney injury. Preliminary data from a recent clinical study found that T2DM patients treated with dapagliflozin for 12 weeks had lower urinary excretion of KIM-1 (related to creatinine) compared with placebo [56]. In another trial, patients with T2DM that were treated with dapagliflozin for 6 weeks had lower urinary excretion of KIM-1, markers of glomerular injury (IgG and IgG4), as well as a marker of inflammation (IL-6) compared with placebo. Moreover, injury markers did not correlate with eGFR changes further supporting the notion that the early decrease in eGFR seen in SGLT2 inhibitor treated individuals does not reflect tubular injury [57].

Chang et al. [58] aimed to determine whether SGLT2 inhibition is detrimental or beneficial in a mouse model of ischemia-reperfusion (IR) injury. The authors found that dapagliflozin administration by oral gavage for 2 days, starting 24 h prior to IR or sham surgery, enhances the HIF1-α-positive area in healthy and IRkidneysections (detected by immunohistochemistry), possibly indicating increased hypoxia [58]. Notably, 24 h after ischemia SGLT2 inhibition and a higher HIF1-α signal were associated with improved renal function (assessed by BUN and serum creatinine) as well as reduced IR-induced tubular injury (assessed by renal cortical vacuolization, peritubular/PT leukocyte infiltration, PT simplification, loss of PT brush border, blebbing of apical membranes, and intraluminal aggregation of cells and proteins). Unfortunately, no detailed HIF1-α localization analysis was performed. Moreover, the study only provided a short-term follow-up and did not explore the effect of later initiation of treatment. More recently, Nespoux et al. [59] induced bilateral renal artery clamping to induce IR injury in mice lacking SGLT1, the glucose transporter expressed in the S3 segment in the OM. Absence of SGLT1 was found protective with evidences at 2 weeks after IR injury of improved recovery of GFR (by FITC-sinistrin) and plasma creatinine levels, better recovery of urine concentration ability and reduced mRNA expression of markers of PT injury, inflammation, and fibrosis [59]. This preliminary data support a potential negative role of renal SGLT1 in the context of IR-induced AKI. Further studies are needed to confirm this and better define the interaction between SGLT2 and SGLT1 in the kidney in health and disease.

Summary and perspectives

Diabetes induces hyperglycemia and tubular growth which, in part via SGLT2, enhance the amount of sodium and glucose reabsorbed by the PT, and increases GFR through the physiology of TGF and tubular back pressure. This results in higher tubular transport work and higher O_2 consumption. SGLT2inhibitorsare anew classofblood glucose lowering drugs that were found renoprotective and reduced the incidence of heart failure in patients with T2DM and high CV risk. SGLT2 inhibitors lower proximal tubular hyperreabsorption of glucose and sodium, and thereby induce an acute functional decrease in GFR. The latter has multiple beneficial effects on the kidney, including the lowering of filtered albumin and renal

transport work and oxygen consumption, which have the potential to better preserve GFR and kidney function in the long term. The associated diuretic and natriuretic effects of SGLT2 inhibition lower blood pressure, volume overload, and body weight which can help protect the failing heart. SGLT2 inhibition shifts transport of sodium and glucose from the cortex to the OM which may make the latter region more vulnerable. However, this may also simulate systemic hypoxia to the oxygen sensor in the deep cortex/OM of the kidney and release more EPO, which, together with the modest diuretic effect, modestly enhances hematocrit thereby facilitating oxygen delivery to the kidney cortex and OM but also to other organs, including the heart. Nevertheless, the use of SGLT2 inhibitors in patients who are at the risk of AKI, such as those who are volume depleted or are receiving drugs that can facilitate the development of AKI, such as radiocontrast agents or NSAIDs, needs further consideration. SGLT2 inhibitors are also being tested in patients with T1DM and, since their effects on GFR, natriuresis, and diuresis can occur in the absence of hyperglycemia, they are also evaluated in non-diabetic patients with heart failure or CKD. Moreover, dual inhibition of SGLT2/SGLT1 as well as selective SGLT1 inhibition is also developed as potential new therapeutic strategies. All these studies will further and critically broaden our understanding of the role of these glucose transporters in health and disease, and of the therapeutic potential of inhibiting the renal reabsorption or intestinal intake of glucose to treat metabolic, renal, and cardiac diseases.

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Abbreviations

ACE	angiotensin-converting enzyme
AKI	acute kidney injury
BUN	blood urea nitrogen
CKD	chronic kidney disease
CV	cardiovascular
eGFR	estimated GFR
EPO	erythropoietin
FAERS	U.S. FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GFR	glomerular filtration rate
IR	ischemia-reperfusion

KIM-1	kidney injury molecule-1
mTAL	medullary thick ascending limb of the loop of Henle
NSAID	non-steroidal anti-inflammatory drug
OM	outer medulla
PT	proximal tubule
RED	Renoprotective Effects of Dapagliflozin in Type 2 Diabetes
SGLT2	sodium-glucose cotransporter 2
SNGFR	single nephron GFR
TGF	tubuloglomerular feedback
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

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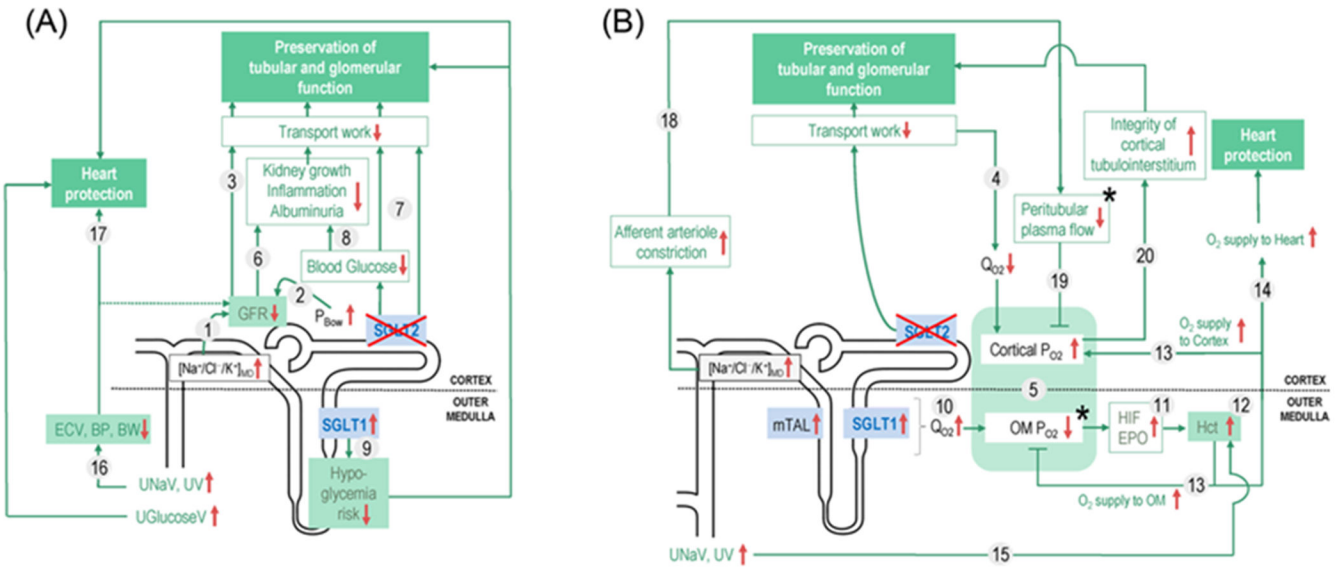

Figure 1. SGLT2 inhibition and kidney protection in diabetes

(**A**) Consequences of SGLT2 inhibition on GFR, tubular transport work, body volume homeostasis, hypoglycemia risk, and the potential role in kidney and heart protection. (**B**) Proposed effects of SGLT2 inhibition on renal cortical and medullary oxygenation and the potential role in kidney and heart protection. SGLT2 blockade reduces diabetes-induced glucose and Na^+ hyperreabsorption in the early PT, thereby increasing NaCl delivery to downstream macula densa which reduces GFR through the physiology of tubu-lo-glomerular feedback (TGF) (1). Osmotic effects of increased luminal glucose concentration increases distal tubular fluid delivery, which lowers GFR by increasing hydrostatic pressure in Bowman's space (P_{Bow}) (2). Reduction in GFR reduces tubular transport work (3), particularly in the proximal convoluted tubule (PCT), thereby lowering cortical oxygen demand (Qo_2) (4), and increasing cortical oxygen tension (P_{O2}) (5). GFR reduction may also attenuate tubular growth and albuminuria and consequently kidney inflammation (6). Lowering blood glucose and cellular SGLT2 blockade itself also lower tubular transport work (7). Less hyperglycemia also reduces tubular growth, albuminuria and inflammation (8). SGLT2 inhibition shifts glucose reabsorption downstream, particularly to the S3 segment where SGLT1 compensates and reduces the risk of hypoglycemia, thereby preventing hypoglycemia-associated renal and CV damage (9). However and in contrast with the cortex, the shift of glucose and Na^+ reabsorption to S3 and medullary thick ascending limb of the loop of Henle (mTAL) segments raises Q_{O2} (10) and lowers P_{O2} in the outer medulla (OM) (5). The latter may make the OM more vulnerable (*). On the other hand, lower medullary P_{O2} may stimulate pathways induced by hypoxia-inducible factor (HIF), including erythropoietin (EPO) (11), thereby increasing hematocrit (Hct) (12) which improves O_2 delivery to kidney medulla and cortex (13) but also to the heart (14). The diuretic and natriuretic effects of SGLT2 inhibition also increase Hct (15) and reduce effective circulating volume (ECV), blood pressure (BP), and body weight (BW)(16), which all can contribute to heart failure protection (17). TGF-induced afferent arteriole constriction not only lowers GFR but may also reduce peritubular plasma flow (18) and thus oxygen delivery (19) thereby lowering P_{O2} (*) and partially offsetting the effect of transport

inhibition by SGLT2 inhibition. The described changes, including a net increase in cortical oxygen availability, may reset the corticointerstitial energy balance and integrity, thereby allowing to better maintain the tubular transport capacity in the long-term, which is a prerequisite to maintain a higher GFR (20). UGlucoseV, urinary glucose excretion; UNaV, urinary sodium excretion; UV, urinary flow rate.