kidney and dialysis

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Review

The Pathophysiological Basis of Diabetic Kidney Protection by Inhibition of SGLT2 and SGLT1

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Abstract: SGLT2 inhibitors can protect the kidneys of patients with and without type 2 diabetes mellitus and slow the progression towards end-stage kidney disease. Blocking tubular SGLT2 and spilling glucose into the urine, which triggers a metabolic counter-regulation similar to fasting, provides unique benefits, not only as an anti-hyperglycemic strategy. These include a low hypoglycemia risk and a shift from carbohydrate to lipid utilization and mild ketogenesis, thereby reducing body weight and providing an additional energy source. SGLT2 inhibitors counteract hyperreabsorption in the early proximal tubule, which acutely lowers glomerular pressure and filtration and thereby reduces the physical stress on the filtration barrier, the filtration of tubule-toxic compounds, and the oxygen demand for tubular reabsorption. This improves cortical oxygenation, which, together with lesser tubular gluco-toxicity and improved mitochondrial function and autophagy, can reduce pro-inflammatory, pro-senescence, and pro-fibrotic signaling and preserve tubular function and GFR in the long-term. By shifting transport downstream, SGLT2 inhibitors more equally distribute the transport burden along the nephron and may mimic systemic hypoxia to stimulate erythropoiesis, which improves oxygen delivery to the kidney and other organs. SGLT1 inhibition improves glucose homeostasis by delaying intestinal glucose absorption and by increasing the release of gastrointestinal incretins. Combined SGLT1 and SGLT2 inhibition has additive effects on renal glucose excretion and blood glucose control. SGLT1 in the macula densa senses luminal glucose, which affects glomerular hemodynamics and has implications for blood pressure control. More studies are needed to better define the therapeutic potential of SGLT1 inhibition to protect the kidney, alone or in combination with SGLT2 inhibition.

Keywords: SGLT2 inhibitor; diabetic nephropathy; chronic kidney disease; tubuloglomerular feedback; proximal tubule; hyperfiltration

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1. Introduction

The number of patients with diabetic kidney disease (DKD), one of the most serious complications in both type I and II diabetic mellitus (T1DM, T2DM), is increasing worldwide [1,2]. DKD is a leading cause of end-stage kidney disease, which requires renal replacement therapy and increases the risk of cardiovascular events [3,4]. Treatment of DKD requires a multi-disciplinary approach, including glycemic, blood pressure, and lipid control. Renin–angiotensin system (RAS) inhibitors have an established role in DKD treatment [5].

More recently, inhibitors of the sodium-glucose co-transporter 2 (SGLT2), which are a new class of anti-hyperglycemic agents, have been demonstrated to be kidney-protective, independent of RAS blockade [6,7]. Clinical trials, which are discussed in more detail below, have demonstrated that SGLT2 inhibitors improve kidney and cardiac outcome in patients with T2DM [8,9]. Moreover, SGLT2 inhibitors protect against chronic kidney

disease (CKD) progression in patients with and without T2DM [10,11]. These findings indicate that SGLT2 inhibitors can protect the kidney, at least in part, independent of their blood glucose-lowering effect.

Besides SGLT2, there is a growing interest in SGLT1 as a therapeutic target, in part because of its role in intestinal glucose reabsorption but also due to its role in the kidney, including a more recently discovered role in glucose sensing at the macula densa, which has implications for glomerular hemodynamics and blood pressure control [12–14].

In this review, we aimed to outline the pathophysiological basis for the inhibition of SGLT2 and SGLT1 to protect from diabetic and non-diabetic kidney disease. For additional information and recent reviews on the topic see refs. [7,12,15–18].

2. The Physiology of SGLT1 and SGLT2 in the Kidney

The human SLC5 solute carrier family comprises 12 members. SGLT1 (SLC5A1) and SGLT2 (SLC5A2) are the most comprehensively characterized members of the SLC5 family, for review see refs. [15,16,19]. SGLT1 was discovered by expression cloning in 1987, and SGLT2 was identified by homology screening in the early 1990s [15,19]. SGLT2 expression is largely restricted to the apical brush border of the early proximal tubule (S1/S2 segments) [16,19,20]. In comparison, renal expression of SGLT1 includes the apical brush border of the later parts of proximal tubules (S2/S3 segment) as well as the apical membrane of the thick ascending limb and the macula densa, as shown in mouse and human kidneys [14,21,22].

The daily amount of glucose filtered by the glomeruli in the healthy human kidney is ~1 mol (~180 g), and basically all the filtered glucose (>99%) is reabsorbed along the tubular system by SGLT2 and SGLT1 [16,19]. The use of genetic and pharmacologic tools in mice indicated that SGLT2 reabsorbs the majority of glucose (97%) in the early proximal tubules whereas SGLT1 reabsorbs the remaining glucose (3%) in the late proximal and further distal tubules [13,20,23]. In accordance, very different kidney phenotypes were observed in individuals with genetic variants in the genes for SGLT1 (*SLC5A1*) and SGLT2 (*SLC5A2*). Humans carrying mutations in SGLT2 present with "Familial Renal Glucosuria" (Online Mendelian Inheritance in Man (OMIM) 233100) characterized by urinary glucose excretion in the range of 1 to 100 g per day, whereas glucose transport in the intestine is normal due to SGLT2 not being expressed in this tissue [24]. In contrast, individuals with mutations in SGLT1 have no or only little glucosuria, but these individuals suffer from "intestinal Glucose Galactose Malabsorption" (OMIM 182380) as a consequence of the decisive contribution of SGLT1 to glucose reabsorption in the intestine [19,25,26].

SGLT2 and SGLT1 use the electrochemical gradient of Na^+ established by the basolateral Na^+/K^+-ATPase. The Na^+-glucose coupling ratio is 1:1 for SGLT2 and 2:1 for SGLT1 [27]. This enhances the ability of SGLT1 to reabsorb glucose in the late proximal tubule despite low luminal glucose concentrations due to the upstream activity of SGLT2. Na^+-glucose cotransport is electrogenic and requires paracellular Cl^- reabsorption or transcellular secretion of K^+ to help maintain the membrane potential and thereby the driving force [28,29]. The glucose reabsorbed by apical SGLT2 and SGLT1 in proximal tubules exits across the basolateral membrane into peritubular capillaries following the glucose concentration gradient that drives facilitative glucose transport through GLUT2 and, to a lesser extent, GLUT1 [16].

3. Potential Upregulation of SGLT2 Expression in the Diabetic Kidney

Hyperglycemia increases the filtration of glucose. To retain the valuable energy substrate, the tubular glucose transport capacity is increased from ~400–500 g/day to ~500–600 g/day in patients with T1DM and T2DM [16,30]. This may involve upregulation of SGLT2 expression as indicated by rodent models of T1DM and T2DM (e.g., refs. [31–33]; for review see refs. [17,34,35]). The increase in SGLT2 expression has been linked to diabetic tubular growth and stimulation of angiotensin (Ang) II and hepatocyte nuclear factor HNF1α [36–38]. Other potential regulators include NF-κB [39] and PKA signaling [40], the

heterogeneous nuclear ribonucleoprotein F (Hnrnpf) [41,42], and nuclear factor erythroid 2-related factor 2 (NRF2) [43]. On the other hand, changes in renal SGLT1 expression appeared less consistent in diabetic rodent models [31,33,44].

Less is known about the kidney expression of glucose transporters in people with diabetes and the information is variable. Greater protein expression of SGLT2 and GLUT2 associated with greater glucose uptake was observed in primary cultures of human exfoliated proximal tubular epithelial cells derived from urine collections of people with T2DM [45]. Higher SGLT2 protein and mRNA expression was also found in fresh kidney biopsies of people with T2DM and advanced nephropathy [46]. In comparison, renal expression of SGLT2 and GLUT2 mRNA were slightly lower in 19 people with T2DM and preserved kidney function versus 20 non-diabetic individuals with similar age and estimated glomerular filtration rate (eGFR) (all subjected to nephrectomy) [47]. Similarly, expression of tubular SGLT2 mRNA in patients with DKD was lower compared with healthy controls or patients with glomerulonephritis [48]. Besides potential differences between SGLT2 protein and mRNA expression, these findings are consistent with the notion that the expression of SGLT2, also in the diabetic kidney, is regulated by multiple factors. This includes metabolic acidosis, hypoxia, and inflammation, which can all suppress the expression of SGLT2 [49–51].

4. SGLT2 Inhibitors Protect Kidney Function in Patients with and without T2DM

The reno-protective effect of SGLT2 in diabetic patients has been established in several clinical trials. In the EMPA-REG OUTCOME Trial in patients with T2DM and preserved renal function (mean eGFR of 74.1 mL/min/1.73 m^2), empagliflozin, as a secondary outcome and in addition to a reduction of cardiovascular events, improved renal outcomes including progression to macroalbuminuria, doubling of serum creatinine concentration, initiation of renal replacement therapy, or death related to kidney disease [52,53]. Similar improvement in secondary renal and cardiac outcomes in patients with preserved kidney function were observed with canagliflozin in the CANVAS and with dapagliflozin in the DECLARE-TIMI58 trial [54,55].

The CREDENCE trial with canagliflozin was the first randomized controlled trial that recruited albuminuric patients with T2DM and an eGFR of 30–90 mL/min/1.73 m^2 [56]. The trial was stopped early and canagliflozin reduced the relative risk of the kidney-specific composite of end-stage kidney disease, a doubling of creatinine concentration, or death due to renal cause by 34%. Canagliflozin also reduced the risk of cardiovascular death, myocardial infarction, and stroke. For the DAPA-CKD study [10], participants with an eGFR of 25 to 75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200 to 5000 were randomly assigned to dapagliflozin or placebo. This study was unique in that non-diabetic patients were also included. Dapagliflozin reduced the worsening of kidney function or death in CKD patients regardless of the presence or absence of type 2 diabetes. Although, a follow up analysis suggested a somewhat better preservation of eGFR in response to dapagliflozin in patients with T2DM and higher HbA1c [57], the findings implied protective mechanisms beyond blood glucose lowering. The EMPA-KIDNEY trial also evaluates the effects of empagliflozin against CKD progression and cardiovascular events in both diabetic and non-diabetic patients [58] and is planned to be ended early because of efficacy of empagliflozin in individuals with CKD.

5. The Metabolic Signature of SGLT2 Inhibition

The logic of inhibiting SGLT2 as a therapeutic strategy in diabetes begins with the role of SGLT2 in glucose retention and maintaining hyperglycemia (Figure 1). SGLT2 inhibitors are associated with a low hypoglycemia risk because these drugs do not interfere with metabolic counterregulation and because they will no longer reduce blood glucose concentration once the amount of glucose that is filtered drops below the transport capacity of SGLT1 (~80 g/day) [16]. SGLT2 inhibitors lower the risk of harmful blood glucose highs and lows, which in combination induce relatively small changes in HbA1c. As part of the

metabolic counter-regulation, carbohydrate utilization is shifted to lipid utilization, which diminishes subcutaneous and visceral fat as well as body weight. The released free fatty acids and the liver formation of ketones deliver extra energy resources to many organs [7] (Figure 1). Losing glucose into the urine together with a metabolic counter-regulation similar to fasting, may offer unique benefits as a blood glucose-lowering strategy.

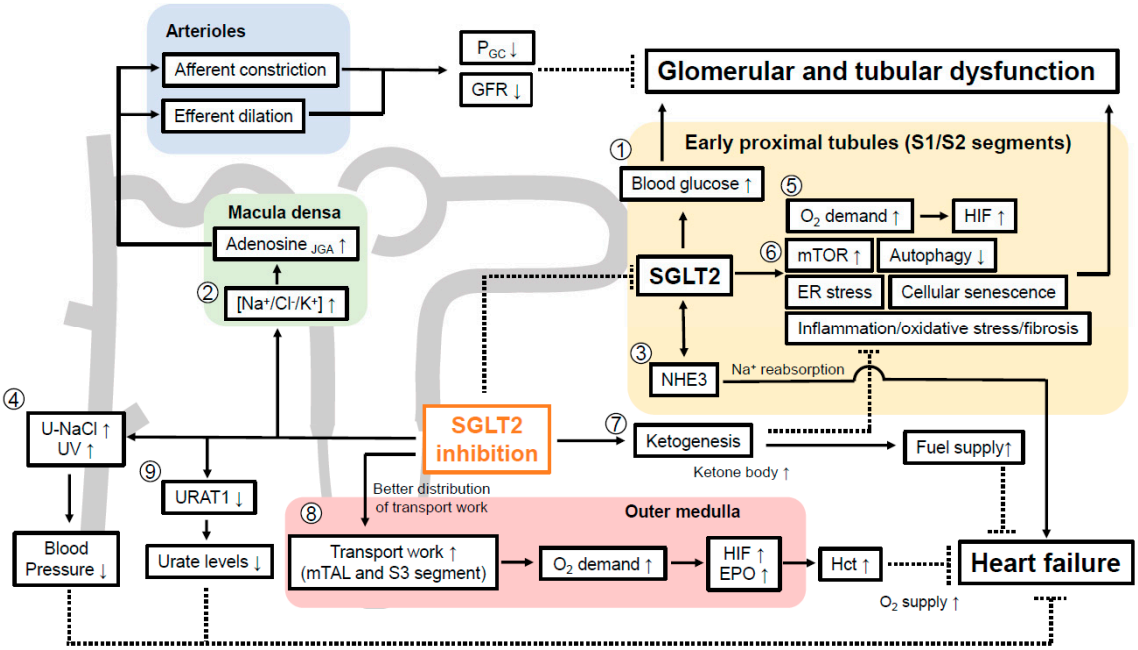

Figure 1. The pleiotropic effects of SGLT2 inhibition. (①) SGLT2 is located in early proximal tubules and reabsorbs the majority of glucose. (②) SGLT2 inhibition increases luminal delivery of sodium chloride to the macula densa, which reduces glomerular capillary pressure (P_{GC}) and GFR through the physiology of the tubuloglomerular feedback (TGF). Locally formed adenosine constricts the afferent arteriole through adenosine A1 receptors in a paracrine manner, but can also dilate the efferent arteriole through adenosine A2 receptors. (③,④) The diuretic (UV) and natriuretic (U-NaCl) effects of an SGLT2 inhibitor as well as its effects on blood pressure and heart failure outcome may in part depend on its functional interaction for Na reabsorption in the early proximal tubule with the Na-H-exchanger NHE3. (⑤) SGLT2 inhibition reduces GFR and thereby the transport load and O_2 consumption, which ameliorates cortical hypoxia and diabetic kidney injury. (⑥) SGLT2 contributes to glucotoxicity and tubular injury via inflammation, cellular senescence, or impaired autophagy. (⑦) SGLT2 inhibition promotes ketogenesis. The increase in ketones is protective against kidney injury and provides energy substrates for many organs including kidney and heart. (⑧) SGLT2 inhibition shifts transport work downstream, better distributes transport, and increases oxygen demand in the outer medulla, which might stimulate hypoxia-inducible factor (HIF) and erythropoietin (EPO), thereby increasing hematocrit (Hct). Hct is also raised by the diuretic effect, and the increased Hct facilitates oxygen delivery to kidney and other organs. (⑨) SGLT2 inhibitors may inhibit urate reabsorption via URAT1, thereby increasing urinary urate excretion and reducing plasma uric acid levels. JGA, juxtaglomerular apparatus.

SGLT2 inhibitors also reduce urate levels. This is due to an increase in kidney urate excretion, which is related to an increase in tubular or urinary delivery of glucose [59–61] (Figure 1). Studies in gene targeted mouse models indicated a role for the luminal urate transporter URAT1 in the acute uricosuric effect of canagliflozin [60]. Similarly, empagliflozin and the URAT1 inhibitor, benzbromarone, both significantly reduced plasma uric acid and increased fractional uric acid excretion in people with T2DM, but the effects were not additive [62].

6. SGLT2 Inhibition Acutely Lowers GFR to Preserve It in the Long-Term

According to the tubular hypothesis of diabetic hyperfiltration [12], the diabetic kidney filters more glucose and the tubules grow. This enhances the tubular transport machinery, including SGLT2, and increases the reabsorption of glucose but also sodium, chloride, and fluid. Lesser luminal delivery of sodium chloride to the macula densa increases GFR and glomerular capillary pressure (P_{GC}) through the physiology of the tubuloglomerular feedback (TGF). The lesser early distal fluid delivery reduces tubular back pressure, which increases filtration pressure, and thereby likewise contributes to the rise in GFR, which serves to stabilize NaCl and fluid delivery to the further distal nephron and urine. The TGF response is mediated by the macula densa release of ATP and local formation of adenosine, which constricts the afferent arteriole through adenosine A1 receptors in a paracrine manner [63]. Increasing the interstitial adenosine tone reduces diabetic glomerular hyperfiltration [64]. Along these lines, SGLT2 inhibition attenuates reabsorption of glucose and increases the delivery of sodium chloride to the macula densa, which lowers GFR (Figure 1). The concept has been established in micropuncture studies in rats [65–67] and the GFR lowering effect of genetic or pharmacologic inhibition of SGLT2 shown in murine diabetes models [33,68]. Direct in vivo visualization techniques showed that empagliflozin reduces the enlarged diameter of glomerular afferent arteries and single nephron GFR in Akita diabetic mice, and the effect of empagliflozin was abolished by pharmacological blockade of adenosine 1 receptors [69]. Recent micropuncture experiments in diabetic rats demonstrated that SGLT2 inhibition indeed lowers P_{GC} and this effect is TGF-dependent. Moreover, the studies observed an inverse relationship between the magnitude of GFR and P_{GC} responses indicating an additional role for efferent arteriole dilation in response to an SGLT2 inhibitor [67] (Figure 1). The acute or short-term GFR-reducing effect of SGLT2 inhibitors were confirmed in individuals with T1DM and T2DM. Moreover, based on associated effects on renal blood flow, vascular resistance, and filtration fraction, the authors proposed effects on the afferent [70] and efferent arteriole [71], respectively.

Most critically, clinical data show that the GFR response to SGLT2 inhibition is biphasic: the GFR initially is reduced but this is followed by long-term GFR preservation [53,56,72–74]. Moreover, following discontinuation of the SGLT2 inhibitor, eGFR increased to baseline levels [53,72]. The initial GFR-reducing effect [56,75,76], the long-term GFR preservation [56] as well as the reversibility after discontinuation of the SGLT2 inhibitor [76] were confirmed in patients with T2DM and CKD stage 2/3. Thus, the early rise in plasma creatinine in response to an SGLT2 inhibitor reflects a "functional and reversible" reduction in GFR, rather than kidney injury. In accordance, dapagliflozin treatment lowered the urinary excretion of markers of glomerular and tubular injury in individuals with T2DM [77,78]. Moreover, meta-analyses of clinical studies came to the conclusion that SGLT2 inhibitors initially cause a small rise in serum creatinine but lower the incidence of acute kidney injury (AKI) [9,79].

7. How can SGLT2 Inhibitors Preserve Kidney Function?

By reducing renal blood flow, GFR, and P_{GC} and increasing tubular backpressure, SGLT2 inhibitors lower the physical stress on the capillaries of the glomeruli and the glomerular filtration of factors that can be toxic to the tubules (including glucose, growth hormones, advanced glycation end products, albumin). The handling of these factors by the tubular system needs energy and facilitates hypoxia, weakens autophagy, and induces oxidative stress, inflammation, and fibrosis, which drive the development and progression of diabetic kidney disease [12,80] (Figure 1).

7.1. SGLT2 Inhibition and Oxygen Handling in the Kidney Cortex

Hypoxia is caused by a mismatch between oxygen demand and delivery. In the kidney, renal perfusion is the primary determinant of oxygen delivery. The principle driver of oxygen demand is the generation of adenosine triphosphate (ATP) that is needed to support the tubular transport processes, including the reabsorption of sodium [81]. The latter is

determined by the amount of filtered sodium thus making GFR the main driver of renal oxygen consumption. Renal hypoxia plays a key role in the pathogenesis of DKD and is the consequence of reduced oxygen delivery due to microvascular damage and increased GFR and thus active sodium and glucose reabsorption on the level of the single nephron [81]. Hypoxia-inducible factor (HIF), a transcriptional factor, has a central role in sensing and adaptation against hypoxia [82]. Studies have demonstrated that chronic activation of HIF exacerbates diabetic kidney injury [83,84].

In accordance with the above, mathematical modeling predicted that SGLT2 inhibition diminishes the oxygen demand of the proximal convoluted tubule of the diabetic kidney, in part by lowering GFR [85,86], and the predicted rise in cortical O_2 pressure was confirmed in diabetic rats in response to the SGLT2/SGLT1 inhibitor phlorizin [87] and with dapagliflozin in albuminuric patients with T1DM [88]. Luseogliflozin suppressed HIF1α expression and oxygen consumption in cultured renal proximal tubular cells treated with hypoxia [89], and, in vivo, reduced renal HIF1α expression and attenuated glomerular and tubular injury in db/db mice [89]. Similarly, dapagliflozin inhibited proximal tubule upregulation of HIF1α in streptozotocin-induced (STZ) diabetic mice and the associated metabolic switch from lipid oxidation to glycolysis [90]. These findings support the hypothesis that SGLT2 inhibition ameliorates hypoxia and the related damage in the kidney cortex in diabetes. Notably, the preservation of cortical, rather than medullary, oxygenation appears to be decisive for the preservation of renal function in patients with CKD [91] (Figure 1).

SGLT2 inhibitors reduce the consumption of O_2 by the kidney cortex due to the direct SGLT2 inhibition and the lowering of GFR [85,86,92] but may also do so as a consequence of a functional coupling of SGLT2 with other transport proteins co-expressed in the brush border of the early proximal tubule. Like SGLT2, the Na^+/H^+ exchanger 3 (NHE3) is located in the brush border of the early proximal tubules [93]. NHE3 contributes to Na^+ and fluid reabsorption but also regulates acid-base balance by mediating bicarbonate reabsorption and ammonia secretion [94]. NHE3 is co-localized with SGLT2 in the early proximal tubule and evidence is accumulating that they functionally interact. SGLT2 inhibition phosphorylated NHE3 in diabetic rats [95] and mice [96] at sites (S552 and/or S605) where phosphorylation is linked to reduced NHE3 activity. Vice versa, tubular NHE3 knockdown reduced kidney SGLT2 expression [51,93]. Empagliflozin also enhanced NHE3 phosphorylation and reduced tubular NHE3 activity in a rat model of heart failure [97]. Furthermore, tubular knockdown of NHE3 in non-diabetic mice inhibited the acute natriuretic effect of empagliflozin and its chronic consequence on blood pressure and kidney renin expression [96]. Collectively, the effect of SGLT2 inhibitors on NHE3 may contribute to lower cortical transport work and may also help to reduce blood pressure and heart failure risk in diabetic and non-diabetic settings [8] (Figure 1).

7.2. Renal Transport Work Is More Equal Distributed by SGLT2 Inhibition and Potential Mimicking of Systemic Hypoxia at the Oxygen Sensor in the Kidney

The early proximal tubule is responsible for a large fraction of glomerular filtrate reabsorption and thus oxygen consumption [85,86]. SGLT2 inhibition shifts some of the NaCl, glucose, and fluid reabsorption to downstream segments. This causes a more equal distribution of the transport workload along the tubular and collecting duct system, and thereby may help the long-term preservation of tubular integrity and function. The increase in downstream transport work in response to SGLT2 inhibition is limited by the accompanied reduction in blood glucose and/or GFR [85,86]. Nevertheless, by shifting more transport to S3 segments and thick ascending limbs, SGLT2 inhibitors may reduce the O_2 availability in the renal outer medulla [85–87]. Moreover, we proposed the hypothesis that this transport shift simulates systemic hypoxia at the oxygen sensor in the deep cortex and outer medulla of the kidney, where it stimulates HIF-1α and HIF-2α [92]. Gene targeting and pharmacological inhibition of SGLT2 enhanced the kidney mRNA expression of hemoxygenase 1 [33,68], which is induced by HIF-1α and a tissue-protecting gene. Upon hypoxia exposure of cells in vitro, HIF-1α and HIF-2α increase Sirt1 gene expression, which

stabilizes HIF-2α signaling and EPO gene expression [98]. Thus, co-stimulation of HIF-1α and HIF-2α in the deep cortex/outer medulla in response to SGLT2 inhibition may explain the observed increase in erythropoietin expression [96] and plasma levels [99,100]. The increase in erythropoietin and the diuretic effect of SGLT2 inhibitors promote a small rise increase in hematocrit and hemoglobin [101], which improves oxygen delivery to the kidney and other organs. Notably, mediation analyses implicated the hematocrit increase as a critical determinant of the benefits of SGLT2 inhibitors on the renal and cardiovascular system [101–103] (Figure 1).

7.3. SGLT2 Inhibitors Promote Mitochondrial Metabolism in the Kidney

In patients with T2DM and albuminuria, dapagliflozin enhanced the urinary excretion of metabolites that are related to mitochondrial metabolism, potentially reflecting that dapagliflozin improved mitochondrial function in the diabetic kidney [104]. Increased urinary metabolites linked to mitochondrial metabolism were also detected in Akita mice in response to empagliflozin [96]. Both ipragliflozin and calorie restriction reduced the renal accumulation of the tricarboxylic acid (TCA) metabolites in the kidney of BTBR ob/ob mice [105]. In non-diabetic and Akita mice, empagliflozin enhanced urinary azelaic acid [96]. The latter is endogenously generated by peroxisomal ω-oxidation pathway from the polyunsaturated essential fatty acid, linoleic acid [106], and has been related to improved mitochondrial biogenesis and autophagy [107]. Moreover, application of azelaic acid reduces adiposity in mice by rewiring the fuel preference to fats [108]. Empagliflozin lowered urinary excretion of stearate and palmitate in non-diabetic and diabetic mice, potentially reflecting renal fuel preference rewiring to fats [96], which has been associated with renal health [109]. In accordance, scRNA-seq of proximal tubules in db/db mice indicated that while RAS blockade is more anti-inflammatory/anti-fibrotic, SGLT2 inhibition affected more genes related to mitochondrial function [110]. Studies in non-diabetic mice provided evidence that SGLT2 inhibition causes distinct effects on kidney metabolism reflecting responses to partial NHE3 inhibition as well as urinary loss of glucose and NaCl; this included upregulation in renal gluconeogenesis and using tubular secretion of the TCA cycle intermediate, alpha-ketoglutarate, to potentially communicate the requirement of compensatory NaCl reabsorption to the distal nephron [96].

7.4. SGLT2 Inhibition Suppresses Tubular mTOR Activity via Enhancing Ketogenesis

Mammalian target of rapamycin complex 1 (mTORc1) acts as a sensor for nutrient state, and regulates the maintenance of cellular homeostasis and growth by promoting mitochondrial synthesis, lipid synthesis, and suppressing autophagy [111]. In the diabetic kidney, hyper-activation of mTORc1 is involved in podocyte and tubular injury [112,113]. Dapagliflozin suppressed the increased mTORc1 activity observed in the tubular lesions of diabetic Akita mice. Furthermore, constitutive activation of mTORc1 in renal proximal tubular cells induced renal fibrosis and abolished the renal-protective effects of dapagliflozin [114]. Moreover, empagliflozin increased ketogenesis and the elevated ketone bodies exerted renoprotective effects on kidney outcome in diabetic mice via suppression of tubular mTORc1 activation [115] (Figure 1).

7.5. SGLT2 Inhibition Increases Tubular Autophagy

Autophagy is a lysosomal degradation pathway that removes dysfunctional components for clearance and reuse. Basal autophagy in the kidney has an important role in maintaining cellular metabolic and organelle homeostasis. On the other hand, dysregulated autophagy can worsen tissue injury under pathological conditions such as DKD [116,117]. Empagliflozin reduced the renal accumulation of p62, an indicator of autophagy activity, suggesting that empagliflozin enhanced autophagy in the diabetic kidney of Akita mice [33]. In vitro, empagliflozin and dapagliflozin inhibited mTOR in renal tubular cells under high glucose condition and increased autophagic activity, which resulted in improved mitochondrial biogenesis [118,119] (Figure 1).

7.6. SGLT2 Inhibition Attenuates Cellular Senescence in Renal Tubular Cells

Cellular senescence, defined as the irreversible cessation of mitosis, is observed in the aged kidney but also critically contributes to DKD pathogenesis [120]. The progression of cellular senescence is associated with decreased telomere length, decreased expression of cyclins and cyclin-dependent kinases (CDKs), and increased expression of CDK inhibitors such as p16 and p21 [120]. Studies using diabetic animals or human kidney biopsy have demonstrated that the expression of CDK inhibitor or senescence-associated β-galactosidase (βGAL) are increased in renal tubular cells [121,122].

SGLT2 inhibitors improve markers of cellular senescence (Figure 1). Empagliflozin lowered renal p21 upregulation in T1DM Akita mice [33]. Using cultured human renal tubular cells, SGLT2 knockdown attenuated the increase of βGAL and p21 caused by high glucose [123]. Dapagliflozin reduced the expression of p16, p21, and p53, another senescence-associated marker, in the kidney of db/db mice. Mechanistically, SGLT2 inhibition induced β-hydroxybutyrate (β-HB), which stimulated NRF2 nuclear translocation and inhibited cellular senescence in human kidney tubular cells [124].

7.7. Evidence That SGLT2 Inhibitor Alleviates ER Stress in Kidney

The endoplasmic reticulum (ER) is the major site for protein folding, maturation, or trafficking to maintain the cellular homeostasis. Disruption of ER homeostasis causes ER stress and facilitates the accumulation of unfolded or misfolded proteins (unfolded protein response, UPR). Various stimuli induce ER stress under diabetic condition, hyperglycemia, oxidative stress, advanced glycation end products, EGFR pathway, or angiotensin II receptor pathways [125,126]. ER stress in kidney cells such as podocytes and tubular cells is involved in the pathogenesis of diabetic nephropathy [127].

Dapagliflozin attenuated renal inflammation and fibrosis which was associated with reduced ER stress markers such as GRP78/BiP and CHOP in high-fat-diet-fed rats [128]. High glucose induced apoptosis through the elf2α-CHOP axis in HK-2 cells, an effect reduced by dapagliflozin. Similarly, dapagliflozin reduced elf2α phosphorylation, ATF4 and CHOP expression as well as caspase 3 activity in the kidney of db/db mice [129] (Figure 1).

7.8. SGLT2 Inhibitors Reduce Inflammation and Oxidative Stress in DKD

Inflammation and oxidative stress contribute to DKD [130]. Cytokines/chemokines and oxidative stress markers such as TNFα-related pathway, MCP1, and 8-OHdG in blood and urine are predictors of DKD progression [131–133]. There are many reports showing anti-inflammatory and anti-oxidative stress effects of SGLT2 inhibitors on kidney injury in Akita, KK-Ay, db/db or BTBR ob/ob diabetic mice or in response to isoprenaline-induced renal oxidative damage in rats [33,44,46,134–137] as well as in cultured cells [118,138,139]. In clinical studies, SGLT2 inhibitors reduced blood levels of high-sensitivity C-reactive protein and inflammatory cytokines in diabetic patients [140]. Moreover, Nod-like receptor protein 3 (NLRP3) inflammasome is a large multiprotein complex that stimulates the secretion of pathogenic inflammatory cytokines, specifically interleukin-1β (IL-1β), and has been implicated in diabetic complications [141]. Empagliflozin reduced macrophage inflammasomes and subsequent IL-1β release in patients with T2DM and high risk for cardiovascular events [142]. Along these lines, the therapeutic effect of dapagliflozin on diabetic kidney injury was associated with decreased expression of inflammasome markers such as NLRP3, ASC, IL-1β, and IL-6 in the kidneys of BTBR ob/ob mice [143] (Figure 1).

7.9. Evidence That SGLT2 Inhibition May Affect EMT to Facilitate Renal Fibrosis

One of the hallmarks of diabetic kidney injury is accumulation of extracellular matrix (ECM) in the glomeruli and tubulointerstitium [144]. Activated myofibroblasts regulate the syntheses and production of ECM. The origin of myofibroblast is diverse and debated; fibroblasts originating from epithelial mesenchymal transition (EMT) may contribute [145],

including in DKD [146] and when exposing cells in vitro to advanced glycation end products or high glucose [147,148].

Dapagliflozin improved renal dysfunction and tubulointerstitial fibrosis associated with less renal STAT1 and TGF-β1 expression in the kidney of STZ-diabetic mice. Dapagliflozin reduced enhanced STAT1 expression in HK-2 cells and prevented downregulation of E-cadherin and α-SMA induction in response to high glucose [149]. Similarly, empagliflozin reduced high glucose-mediated oxidative stress, EMT, and fibrosis process in HK2 cells [150]. High glucose suppressed Sirt3, promoted aberrant glycolysis, and caused EMT in kidney tubular cells, and SGLT2 inhibition corrected these changes and ameliorated renal damage [151] (Figure 1).

8. The Pathophysiological Basis for Inhibiting SGLT1 in DKD

8.1. Compensatory Glucose Uptake by Tubular SGLT1 When SGLT2 Is Inhibited

As described above and under normal conditions, SGLT1 contributes only little to kidney glucose reabsorption (approximately 3%). However, the contribution of glucose reabsorption via SGLT1 can increase substantially when more glucose is delivered downstream of the early proximal tubule (Figure 2). Studies using selective SGLT2 inhibition or gene knockout in combination with mice lacking SGLT1 demonstrated that SGLT1-mediated glucose reabsorption explains all renal glucose reabsorption during SGLT2 inhibition; the studies uncovered a significant glucose transport capacity of SGLT1, ~40–50% of filtered glucose in euglycemia, that is not engaged under normal conditions with intact upstream SGLT2 [20,23,152]. Adding an SGLT1 inhibitor is expected to improve glycemic control when treatment with an SGLT2 inhibitor alone is inadequate, e.g., in patients with more advanced impairment in kidney function, and both the renal and intestinal (see below) contribution of SGLT1 inhibition should be sizable.

On the downside, dual SGLT2/SGLT1 inhibition (especially if the SGLT1 inhibitor also reaches and targets the tubular S2/3 segment) may increase the hypoglycemia risk, and the enhanced diuresis could enhance the risk of hypotension, pre-renal failure, complications from hemoconcentration, and diabetic ketoacidosis. Notably, SGLT1 inhibition in the ventromedial hypothalamus of rats improves the hypoglycemia-induced counterregulatory responses [153], and studies in patients with T1DM found that the dual SGLT2/SGLT1 inhibitor, sotagliflozin, lowered the hypoglycemia risk [154].

Oral application of certain doses of the dual SGLT2/SGLT1 inhibitor sotagliflozin and the selective SGLT1 inhibitor GSK-1614235 inhibit glucose transport in the intestine in the absence of severe gastrointestinal side effects [155,156], which may indicate a potential therapeutic window for partial intestinal SGLT1 inhibition [18]. Moreover, SGLT1 inhibition in the intestine improves glucose homeostasis not only by inhibiting/delaying the uptake of glucose but also by an indirect effect that involves a sustained intestinal release of glucose-lowering incretin hormones, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [18,157,158] (Figure 2). GLP-1 receptor agonists are approved as anti-hyperglycemic drugs and have kidney protective properties [159]. To which extent GLP-1 quantitatively contributes to the metabolic or any potential kidney protective effect of SGLT1 inhibition remains to be determined.

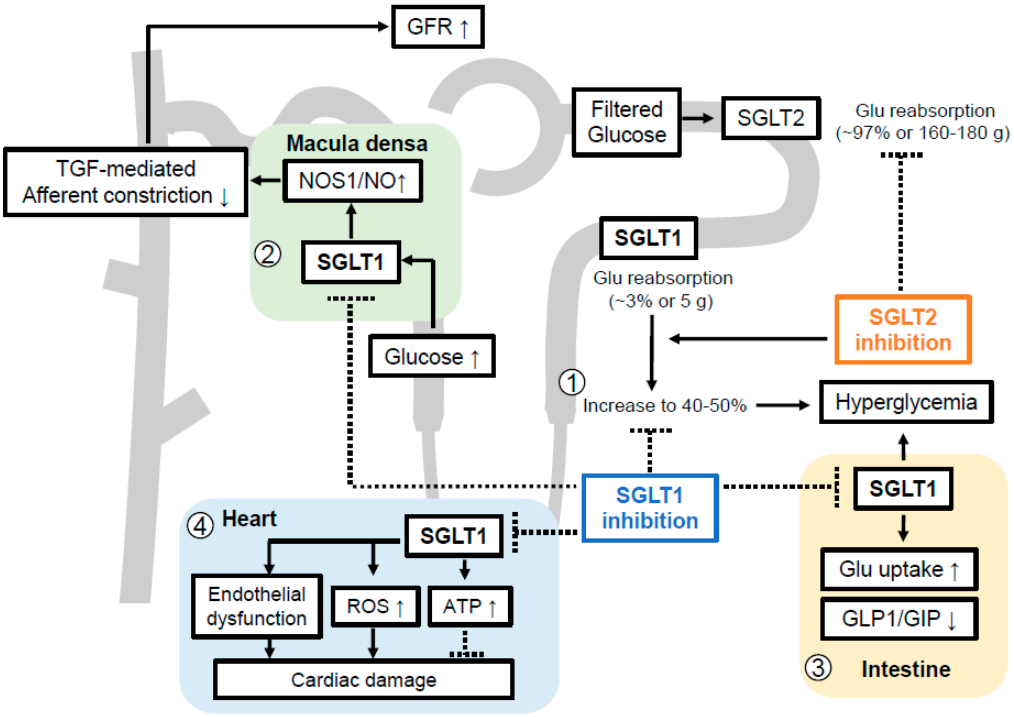

Figure 2. The pathophysiologic roles of SGLT1. (①)Compensatory glucose uptake (up to 40–50% of filtered glucose in euglycemia) by tubular SGLT1 when SGLT2 is inhibited. (②) Increased tubular glucose delivery is sensed by SGLT1 in macula densa cells, which increases NOS1-dependent NO formation. NO reduces TGF-induced afferent arteriolar constriction, thereby contributing to glomerular hyperfiltration. (③) SGLT1 in intestine promotes glucose (Glu) uptake and attenuates GLP1 and GIP release, which worsen glycemic control in diabetic condition. (④) SGLT1 in heart can be protective or harmful in cardiac complications via replenishing ATP, increasing reactive oxygen species (ROS) formation, or impairing endothelial function, respectively. An SGLT1 inhibitor has the potential to counter the SGLT1-mediated effects.

8.2. Macula Densa SGLT1-NOS1 Pathway Determines Glomerular Hyperfiltration and Blood Pressure Regulation in Diabetic Setting

The macula densa (MD) expresses neuronal nitric oxide synthase 1 (NOS1), which forms nitric oxide (NO) to reduce the tone of the afferent arteriole, causes a rightward shift of the TGF curve, and makes the latter less steep around the operating point; all these effects enhance GFR and the delivery of NaCl downstream of the MD and into the urine [160–163]. MD-NOS1 contributes to the rise in GFR in response to acute hyperglycemia, as shown in STZ-induced diabetes in rats and mice, and in Akita and db/db mice [14,164–168]. The stimulus for NOS1 activation in the MD in response to high blood glucose levels is the enhanced tubular delivery of glucose that is sensed by the MD via SGLT1 expressed in the luminal membrane (expression confirmed in mice and humans) [13,14,168] (see Figure 2). As a consequence, enhancing glucose delivery to the macula densa in the isolated perfused juxtaglomerular apparatus attenuated TGF-induced afferent arteriolar constriction, and this attenuation was prevented by pharmacological inhibition of SGLT1 [14]. Moreover, absence of SGLT1 prevented the Akita diabetes-induced upregulation in MD-NOS1 expression and inhibition of TGF [13,168], and reduced glomerular hyperfiltration in Akita and STZ-diabetic mice [13]. Akita mice that lack SGLT1 presented with lesser glomerular hyperfiltration, but also showed lesser weight of the kidneys, smaller glomeruli, and reduced albuminuria [13], leading to the hypothesis that MD-SGLT1 orchestrates the function and structure of the single nephron [12].

In the diabetic kidney, GFR rises, at least in part, to limit NaCl and fluid retention in response to a primary increase in proximal reabsorption [12]. When glucose delivery to the

MD is increased, this indicates saturation of upstream SGLTs and thus hyperreabsorption of sodium, glucose, and fluid. In this setting, the SGLT1-NOS1-GFR mechanism increases GFR to stabilize urinary excretion of sodium and fluid and, thereby, volume balance. Inhibition of this compensatory rise in GFR in the absence of offsetting the primary hyperreabsorption is predicted to enhance blood pressure, which is a first-order mechanism to maintain sodium homeostasis [169]. In fact, absence of SGLT1 not only blunted diabetes-induced glomerular hyperfiltration but lowered renal renin mRNA expression, indicating volume expansion, and increased systolic blood pressure [13]. This is reminiscent of the effects of a selective NOS1 inhibitor in diabetic rats [164] or macula densa-specific NOS1 deletion in db/db mice [167]. In this regard, a weakening of the MD-SGLT1-NOS1-GFR pathway could contribute to the transition from an early hyperfiltering and normotensive diabetic patient to later stages of disease that are associated with GFR loss and hypertension [13,14].

Studies in T1DM Akita mice have shown that combined inhibition of SGLT1 and SGLT2 has additive effects on the early diabetic kidney, including kidney glucose reabsorption, blood glucose control, GFR, glomerular size, and kidney weight [13]. As expected, SGLT2 inhibition raised the expression of MD-NOS1 in non-diabetic mice, and this effect was prevented by SGLT1 knockout [13]. Further studies are required to define the nuances of MD glucose sensing, its effects on the afferent and potentially efferent arterioles and glomerular integrity through MD-NOS1, and the therapeutic implications of this pathway for selective and combined SGLT1 and SGLT2 inhibition.

8.3. Potential Roles of SGLT1 beyond Intestine and Kidney

In many species including human, SGLT1 protein expression is not restricted to the intestine and kidney, but found in parotid and submandibular salivary glands, liver, lung, skeletal muscle, heart, endothelial cells, pancreatic alpha cells, and brain [18]. Little is known about SGLT1 and its inhibition in most of these organs. Rodent studies suggested that the inhibition of SGLT1 in the diabetic heart could be a two-edged sword (for review see ref. [18]): SGLT1 may contribute to cardiomyopathy in diabetes by promoting the accumulation of glycogen in cardiomyocytes and/or driving reactive oxygen species formation; SGLT1, however, may also have protective effects against ischemia reperfusion injury by restoring ATP in the ischemic heart through increasing the glucose supply (Figure 2). It is remarkable that SGLT1 inhibition seems to have beneficial effects in cardiac and kidney ischemia-reperfusion injury [170,171]. In patients with T2DM and CKD, with or without albuminuria, the dual SGLT2/SGLT1 inhibitor sotagliflozin lowered the risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure compared with placebo and was associated with adverse events, including diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis [172]. Kidney outcome data were not conclusive, possibly because the trial ended early owing to loss of funding. Notably, unpublished data from the SCORED trial presented at American College of Cardiology's (ACC) 70th Scientific Session suggested that sotagliflozin may lead to reductions in cardiovascular death, myocardial infarction, and stroke regardless of cardiovascular disease presence, which could reflect a unique role of SGLT1. The quantitative contribution of SGLT1 versus SGLT2 inhibition in the beneficial and adverse effects of sotagliflozin, other than diarrhea, remains to be determined.

9. Conclusions

The nephroprotective effects of SGLT2 inhibitors are independent of pre-existing CKD and, at least in part, independent of their blood glucose-lowering effect. SGLT2 inhibitors induce pleiotropic effects that affect systemic and kidney metabolism as well as glomerular hemodynamics and tubular functions which together have consequences on blood pressure, hematocrit, and tubular and glomerular integrity and health. SGLT1 inhibition improves glucose homeostasis by delaying intestinal glucose absorption and by increasing the release of gastrointestinal incretins. Combined SGLT1 and SGLT2 inhibition has additive effects on renal glucose excretion and blood glucose control. SGLT1 in the macula densa senses

luminal glucose, which affects glomerular hemodynamics and has implications for blood pressure control. The SGLT2 inhibitors empagliflozin, canagliflozin, and dapagliflozin, which have been used for the major outcome studies, vary to some extend in their selectivity for SGLT2 versus SGLT1 but they are still considered relative specific SGLT2 inhibitors. In addition, the clinical studies do not provide clear evidence for relevant differences in relevant outcomes. It will be important to take a close look at compounds that have a stronger effect on SGLT1 at therapeutic doses, such as sotagliflozin, or compounds with a selective effect on SGLT1 to better understand the clinical relevance of SGLT1 inhibition. Thus, more studies are needed to better define the therapeutic potential of SGLT1 inhibition alone or in combination with SGLT2 inhibition. Nuances of the outcome may depend on whether the drug actually reaches SGLT1 in the tubular system or primarily targets intestinal and cardiac SGLT1. The efficacy of selective SGLT2 and dual SGLT1/2 inhibitors is also explored in people with T1DM as add on to insulin. Overall, these drugs improve glycemic control [173–176] and are predicted to show benefits similar to those reported in T2DM [177]. Caution is required due to the greater risk of diabetic ketoacidosis in people with T1DM [174,178]. Since most of the described effects can occur in the absence of hyperglycemia, SGLT2 inhibitors are increasingly being tested in non-diabetic patients with CKD.

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