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Renoprotective Effects of SGLT2 Inhibitors

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INTRODUCTION

Since 2008, the US Food and Drug Administration (FDA) has required proof of cardiovascular (CV) safety for new glucose-lowering therapies[1]. This also affected the development of inhibitors of the sodium glucose cotransporter SGLT2 and produced large-scale clinical trials that were designed to confirm CV safety, but also provided, as secondary outcomes, first insights on kidney outcome. Indeed, three large clinical outcome trials in patients with T2DM and relatively well-preserved kidney function reported that the SGLT2 inhibitors empagliflozin, dapagliflozin and canagliflozin not only reduced the incidence of heart failure but also induced salutary effects on the kidney, including lower hazard ratios (HRs) for major decline in estimated GFR (eGFR)[2–5]. Subanalyses of these trials and systematic review and meta-analysis of multiple randomized controlled trials with various SGLT2 inhibitors indicated that the beneficial effects may extend to patients with T2DM and chronic kidney disease (CKD)[6,7], which was subsequently formally established for canagliflozin in the CREDENCE trial[8]. The DAPA-CKD trial then revealed that dapagliflozin protected the kidneys from failing relative to placebo among patients with CKD, regardless of the presence or absence of T2DM[9], while a follow up analysis suggested that the eGFR preserving effect of dapagliflozin was somewhat greater in patients

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Disclosure Statement

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with T2DM and higher HbA1c[10]. Together, the data indicate that SGLT2 inhibitors can protect the kidney independent of kidney function and T2DM, and that T2DM and/or hyperglycemia enhance the protective effects.

In the following the kidney physiology of SGLT2 is briefly introduced, followed by the discussion of potential renoprotective effects of SGLT2 inhibitors.

THE PHYSIOLOGY OF SGLT2 AND ITS EXPRESSION IN THE DIABETIC KIDNEY

In euglycemia and with normal GFR, the proximal tubule reabsorbs almost all of the filtered glucose (~180 grams/day) and thereby prevents glucose and thus valuable calories (~1/3 of the body's caloric expenditure) from being lost into the urine. The bulk of tubular glucose uptake (>90%) is mediated by high capacity SGLT2 in the "early" proximal tubule (S1/S2 segments) (Figure 1), while the glucose that escapes SGLT2 is "mopped up" by the lower capacity SGLT1 in the "late" proximal tubule (S2/S3 segments)[[11–13] and for review[14,15]] (Figure 2). Glucose exits proximal tubules passively through basolateral GLUT2 (Figure 1).

The kidneys are programmed to retain the valuable energy substrate, glucose, and increase their glucose reabsorption capacity from ~400–450g/day to ~500–600g/day in patients with T2DM and T1DM[14](Figures 1). Studies in humans with T2DM[16–18] and genetic rodent models of T2DM and T1DM[16,19–21] indicate an upregulation of renal SGLT2 protein expression. Upregulation of SGLT2 expression has been linked to the overall growth and hypertrophy of the diabetic proximal tubule[22], activation of renal sympathetic innervation[23,24] and Ang II AT1 receptors[25] as well as the transcription factor, hepatocyte nuclear factor HNF-1α[26], which may respond to basolateral hyperglycemia sensed through GLUT2[16](Figure 1). The sympathetic nervous system and HNF-1α and HNF-3β have also been implicated in up-regulation of basolateral GLUT2[27,28]. Moreover, insulin phosphorylates and increases SGLT2 activity[29], and postprandial insulin release and hyperinsulinemia due to obesity and type 2 diabetes may increase renal SGLT2 activity to retain increased amounts of filtered glucose (Figure 1). In contrast, conditions with enhanced proximal tubule gluconeogenesis can reduce SGLT2 expression indicating negative feedback by cytosolic glucose[30]. As a consequence, renal SGLT2 expression can be unchanged or reduced in individuals with T2DM as a consequence of enhanced gluconeogenesis (e.g., due to metabolic acidosis or increased sympathetic tone), or due to tubular hypoxia or injury[14] (Figure 1).

THE METABOLIC SIGNATURE OF SGLT2 INHIBITION

The logic of inhibiting SGLT2 as a therapeutic strategy in diabetes starts with the role of SGLT2 in glucose retention and maintaining hyperglycemia (Figure 1). SGLT2 inhibitors do not share the deleterious effects of other anti-hyperglycemic agents like an increase in body weight or hypoglycemia risk, which may offset the benefits of improving glycemic control[31]. SGLT2 inhibitors do not increase the incidence of hypoglycemia[32] because they stop lowering blood gucose once the filtered glucose load falls to the transport capacity of SGLT1 (~80g/day)[12,14]. Furthermore, SGLT2 inhibitors leave metabolic counterregulation

intact, including the upregulation of gluconeogenesis in liver[32] and kidney[33](Figures 1+2). Thus, SGLT2 inhibitors can improve renal and cardiovascular outcome by preventing deleterious blood glucose highs and lows, which together cause only small changes in HbA1c.

SGLT2 inhibition shifts substrate utilization from carbohydrates to lipids, thereby reducing body fat, including visceral and subcutaneous fat[32](Figure 2). The released free fatty acids are used for hepatic formation of ketone bodies, which provide additional energy substrates for many organs, including the kidney epithelia[34–36](Figures 1+2).

It appears that spilling glucose and calories into the urine, which triggers metabolic counterregulation similar to fasting, provides unique benefits as an anti-hyperglycemic approach, possibly because the body's responses to environments with scarce energy resources have been intensely tested and refined during evolution for the survival of the organism[32]. The following sections discuss direct and indirect kidney protecting effects of SGLT2 inhibition that are, at least in part, independent of blood glucose lowering and have the potential to protect the kidney also in the non-diabetic setting.

SGLT2 INHIBITION LOWERS GFR INITIALLY TO PRESERVE IT IN LONG-TERM

As the proximal tubule in the diabetic kidney grows and reabsorbs more glucose through SGLT2 and SGLT1, it also retains more sodium, followed by chloride and fluid. This lowers the delivery of Na, Cl and K to the macula densa (MD), which, through the physiology of tubuloglomerular feedback (TGF), causes single nephron GFR (SNGFR) to increase in order to partially restore fluid and NaCl delivery to the early distal tubule and thereby urine excretion. Hyperreabsorption of fluid in the proximal tubule also reduces the tubular back pressure in Bowman space (P_{Bow}) thereby further increasing filtration pressure and SNGFR. These mechanisms form the basis for the tubular hypothesis of glomerular hyperfiltration in the diabetic kidney[22,37].

Accordingly, inhibition of SGLT2 lowers proximal tubule hyperreabsorption in the diabetic kidney, enhances tubular back pressure and the delivery of Na, Cl and K to the MD, and via TGF reduces glomerular hyperfiltration (Figures 2). This concept has been established by micropuncture studies in hyperfiltering diabetic rats[37–39]. Moreover, pharmacologic or genetic inhibition of SGLT2 reduced glomerular hyperfiltration in diabetic mice[19,20,40], and the GFR lowering effect was independent of effects on blood glucose[20,37,39].

The GFR lowering effect of short-term SGLT2 inhibition was confirmed in humans with T1DM and T2DM[41]. Most importantly, clinical studies have established a biphasic GFR response to SGLT2 inhibition: the initial GFR reduction is followed by long-term GFR preservation[4,8,42–44]. Moreover, after discontinuation of treatment, eGFR increased to baseline in the SGLT2 inhibitor groups[4,42]. The short-term GFR lowering effect[8,45,46], the long-term GFR preservation[8] as well as the reversibility after discontinuation of the SGLT2 inhibitor[46] was confirmed in patients with T2DM and CKD level 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 decreased urinary levels of markers of glomerular and tubular injury in T2DM patients[47,48]. Moreover, meta-analyses of clinical studies concluded that SGLT2 inhibition induces small increases in serum creatinine but reduces the incidence of acute kidney injury (AKI)[49,50].

DOES SGLT2 INHIBITION LOWER GLOMERULAR CAPILLARY PRESSURE?

When MD cells sense an increase in luminal NaCl, the resulting TGF-induced ATP release promotes local formation of adenosine, which primarily constricts the afferent arteriole via adenosine A1 receptors[51] but can also dilate the efferent arteriole via adenosine A2 receptors[52–54](Figure 2). Both effects are expected to lower glomerular capillary pressure (P_{GC}). Studies in mice with T1DM confirmed adenosine A1 receptor-mediated afferent arteriolar vasoconstriction in response to empagliflozin[55](Figure 2). Micropuncture of glomerular capillaries in rats with T1DM established that the SGLT2 inhibitor ipragliflozin indeed reduced P_{GC}[38]; notably, the changes in P_{GC} and GFR were not strictly correlated. This finding cannot be explained by a sole effect on the afferent arteriole, but implied that SGLT2 inhibition constricted the afferent arteriole and also dilated the efferent arteriole[38], and is consistent with the asymmetry of afferent and efferent arteriolar TGF responses and their consequences on GFR and P_{GC}[38,56–58]. As a consequence, SGLT2 inhibition can induce a robust reduction in P_{GC} even when GFR decreases only slightly and vice versa[38]. This may have implications in advanced CKD (GFR<30 ml/(min × 1.73m^2)), where the initial GFR drop in response to SGLT2 inhibition can be small, but the kidney protective effect is preserved[59], possibly due to a robust effect on the efferent arteriole and predominant reduction in P_{GC}[38].

It was recently discovered that the MD senses an increased glucose delivery via luminal SGLT1, which then activates nitric oxide synthase 1 (NOS1), and the resulting increase in NO formation blunts the afferent arteriolar vasoconstrictor effect of TGF and thereby contributes to diabetic hyperfiltration[40,60]. Thus, the increase in MD glucose delivery in response to an SGLT2 inhibitor can activate the MD-SGLT1-NOS1 pathway and attenuate the initial GFR reduction (for details and discussion see[22,40]). Considering the close proximity of the MD to both afferent and efferent arteriole, it is also possible that the MD-SGLT1-NOS1 pathway dilates the efferent arteriole, potentially in settings with low endogenous efferent NO tone.

HOW CAN LOWERING GFR AND PGC PROTECT THE KIDNEY IN LONG-TERM?

By reducing GFR and P_{GC} (and increasing P_{Bow}), SGLT2 inhibition reduces the physical stress on glomerular capillaries and diminishes the glomerular filtration of tubulo-toxic factors (e.g., albumin, growth hormones, advance glycation end products). The interaction of these factors with the tubular system requires energy and promotes hypoxia, impairs autophagy, and triggers renal oxidative stress, inflammation and fibrosis, and thereby the development and progression of diabetic kidney disease[22,61](Figure 2).

The preservation of cortical oxygenation appears to be critical to preserve kidney function in patients with CKD[62]. GFR is the primary determinant of renal NaCl reabsorption and, thus, of renal transport work and oxygen consumption. According to the tubular hypothesis of diabetic kidney disease, lowering single nephron glomerular hyperfiltration and thereby the oxygen-consuming transport work has the potential to preserve the integrity of the remaining nephrons and overall kidney function in the long-term[22](Figure 2). This has been proposed for blockers of angiotensin II and now for SGLT2 inhibitors, and the clinical trials provided evidence that the two strategies are additive and apply to patients with initial GFRs of at least 30 ml/min/1.73 m^2 of body-surface area[22]. Mathematical modeling predicted that SGLT2 inhibition in the diabetic kidney reduces oxygen consumption in the proximal convoluted tubule and renal cortex, in part by lowering GFR[63,64]. SGLT2 inhibition attenuated the cortical tubular expression of hypoxia-induced factor HIF-1α in a murine model of T2DM[65], and the predicted increase in cortical O_2 pressure has been observed in a diabetic rat model using the SGLT inhibitor phlorizin[66] and with dapagliflozin in albuminuric patients with T1DM[67].

SGLT2 inhibitors lower cortical O_2 consumption as a consequence of direct SGLT2 inhibition and the lowering of GFR[63,64,68] but may also do so as a consequence of a functional coupling of SGLT2 to other transporters in the early proximal tubule (Figure 1&2). This has been proposed for the Na-H-exchanger NHE3, such that pharmacological blockade of SGLT2 partially inhibits NHE3 activity[33,69–72]. Vice versa, tubular knockdown of NHE3 reduces SGLT2 expression[30]. The effect of an SGLT2 inhibitor on NHE3 may involve the scaffolding protein MAP17[73], phosphorylation of NHE3[33,70,72,74], but also lower insulin levels (Figure 1&2). Hyperinsulinemia is known to co-stimulates SGLT2, NHE3 and URAT1 in the proximal tubule[14](Figure 1). This may facilitate glomerulo-tubular balance during post-prandial increases in GFR and insulin; but also lead to renal NaCl and urate retention in obesity and T2DM[14] (Figures 1+2). Co-inhibition of NHE3 by SGLT2 inhibitors would enhance the natriuretic effect and lower the O_2 demand also in the non-diabetic setting[33,70,75].

SGLT2 INHIBITORS ACTIVATE METABOLIC COUNTERREGULATION SIMILAR TO FASTING AND REDUCE PROXIMAL TUBULE GLUCO-TOXICITY

By losing glucose into the urine and activating metabolic responses similar to fasting, SGLT2 inhibitors may provide unique benefits[32]. An emerging hypothesis links this to improved autophagy in the kidney and other organs[19,76–79] (Figures 1&2). Empagliflozin reduced the renal accumulation of p62 in Akita mice, providing the first evidence that SGLT2 inhibition may improve autophagy in the diabetic kidney[19](Figure 1). According to the theory, SGLT2 inhibitors reduce blood glucose and insulin levels, lower the cellular glucose availability, and stimulate a starvation-like response, which is induced independent of basal hyperglycemia. The response includes SIRT1/AMPK activation and inhibition of the AKT/mTOR1 pathway, thereby counteracting the primary pathophysiology of the proximal tubule in diabetes and overnutrition[16,35,77,79,80] and inducing autophagy, which promotes cellular defense and pro-survival mechanisms. Autophagy improves energy

metabolism and fuel supply and reduces oxidative stress, cytotoxicity and inflammation (Figure 1).

Preliminary studies in T1DM Akita mice and patients with T2DM, showed that diabetes increased the urinary ratio of lactate to pyruvate, potentially indicating a metabolic shift from mitochondrial oxidation to more glycolysis, an effect reversed by SGLT2 inhibition[81]. In patients with T2DM and albuminuria, dapagliflozin increased urinary metabolites linked to mitochondrial metabolism, potentially indicating that dapagliflozin improves mitochondrial function in the diabetic kidney[82]. 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[83]. Moreover, the SGLT2 inhibitor ipragliflozin reversed the tubular and mitochondrial damage caused by high-fat diet in mice, independent of blood glucose levels[84]. 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 tricarboxylic acid (TCA) cycle intermediate, alpa-ketoglutarate, to communicate to the distal nephron the need for compensatory NaCl reabsorption[33].

SGLT2 inhibitors increase urate excretion and lower plasma urate levels; this response is related to the rise in tubular or urinary glucose delivery[85–87]. Studies in gene targeted mouse models indicated a role for the luminal urate transporter URAT1 in the acute uricosuric effect of canagliflozin[86], which may involve lowering of insulin levels[86,88] or other coupling mechanisms between SGLT2 and URAT1 (Figures 1&2).

SGLT2 INHIBITION CAUSES MORE EQUAL DISTRIBUTION OF RENAL TRANSPORT WORK AND MAY MIMIC SYSTEMIC HYPOXIA AT THE RENAL OXYGEN SENSOR

The early proximal tubule is responsible for a large fraction of glomerular filtrate reabsorption and thus oxygen consumption[63,64]. SGLT2 inhibition shifts some of the glucose, NaCl and fluid reabsorption downstream, and thereby more equally distributes the transport burden along the tubular and collecting duct system, which may help to preserve tubular function in the long-term. The shift in transport to the S3 segment and thick ascending limb in the renal outer medulla, however, may reduce the O_2 availability in this region[63,64,66](Figure 2). The increase in urinary adenosine excretion in patients with T1DM[89] and T2DM[90] in response to SGLT2 inhibition likely reflects an increase in transport work in downstream segments, which enhances ATP consumption and adenosine formation and release in an effort to balance medullary O_2 consumption and supply[53]. The increase in downstream transport work in response to SGLT2 inhibition is also limited by the reduction in blood glucose and/or GFR[63,64](Figure 2). Moreover, we proposed that the transport shift induced by SGLT2 inhibition 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[68]. Gene knockout and pharmacological inhibition of SGLT2 increased the renal mRNA expression of hemoxygenase 1[19,20], a tissue protective gene induced by HIF-1α.

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[91]. Thus, co-stimulation of HIF-1α and HIF-2α in response to SGLT2 inhibition may explain the observed increase in erythropoietin expression[33] and plasma levels[92,93]. Together with the diuretic effect, the latter may contribute to the observed modest increase in hematocrit and hemoglobin in response to SGLT2 inhibition[94], which can improve the oxygenation of renal outer medulla and cortex and facilitate oxygen delivery to other organs (Figure 2). Mediation analyses identified the rise in hematocrit was a key determinant of renal and cardiovascular benefits of SGLT2 inhibition[94–96]. Modelling studies predict that the transport shift to the outer medulla and the natriuretic and diuretic effect of SGLT2 inhibition is in part preserved in CKD due to a high glucose load on the single nephron level (facilitated by lesser blood glucose lowering effect), which induces paracellular sodium secretion in the proximal tubule[68]. This may contribute to the preserved protective effects of SGLT2 inhibitors in patients with CKD.

PERSPECTIVES

Much needs to be learned about the mechanisms involved in kidney protection by SGLT2 inhibitors. The sympathetic nervous system (SNS) plays a deleterious role in the pathogenesis of CKD and is activated by classic diuretics, and this activation is absent with SGLT2 inhibitors in human and animal studies but the mechanism remain unclear[97–102]. There is also a need to better understand the consequences of SGLT2 inhibition on macula densa glucose delivery, their effects on glomerular hemodynamics through the efferent arteriole, and how pathophysiological conditions affect these responses. We need to further unravel the metabolic responses on the cellular level of the early proximal tubule as well as the consequences in downstream segments, including the stimulation of erythropoietin. All this information will be helpful to learn more about the patient populations that benefit from the treatment with SGLT2 inhibitors.

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Key Points:

- At onset of therapy, SGLT2 inhibitors lower glomerular capillary pressure and filtration rate, which reduces the physical stress on the filtration barrier, the exposure of the tubular system to albumin and nephrotoxic compounds, and the oxygen demand for reabsorbing the filtered load
- The metabolic adaptation to urinary glucose loss resembles a fasting response and includes enhanced lipolysis and hepatic formation of ketone bodies, which serve as additional fuel for the kidney
- SGLT2 inhibitors reduce gluco-toxicity in the early proximal tubule associated with improved mitochondrial function and autophagy, which helps preserve tubular transport integrity and function and, thereby, GFR in the long-term
- SGLT2 inhibitors better distribute transport work along the nephron, which may mimic systemic hypoxia at the kidney oxygen sensors in the deeper cortex and outer medulla, thereby stimulating erythropoiesis, which, together with their diuretic effect, enhances hematocrit and improves oxygen delivery to kidneys and other organs

SYNOPSIS

SGLT2 inhibitors can protect the kidneys of patients with and without type 2 diabetes from failing. This includes blood glucose dependent and independent mechanisms. SGLT2 inhibitors lower glomerular pressure and filtration, thereby reducing the physical stress on the filtration barrier 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 and pro-fibrotic signaling and preserve tubular function and GFR in long-term. By shifting transport downstream, SGLT2 inhibitors may mimic systemic hypoxia and stimulate erythropoiesis, which improves oxygen delivery to the kidney and other organs.

Clinical Care points

- Patients must be counseled to monitor their blood pressure and diabetic patients also their blood glucose when initiating SGLT2 inhibitors.
- In the absence of an alternate cause of AKI or hemodynamic instability, the initial decline in eGFR of up to 30% after SGLT2i initiation is expected and likely due to nephro-protective reduction in intraglomerular pressure.
- Due to the glucosuric effect of SGLT2 inhibitors and the associated increased risk of genital mycotic infections, patients must be counseled regarding maintenance of genital hygiene
- To prevent diabetic ketoacidosis, hypovolemia, and hypotension, patients must be instructed to pause taking SGLT2 inhibitors when their oral food and water intake is reduced due to underlying illness or planned surgery.

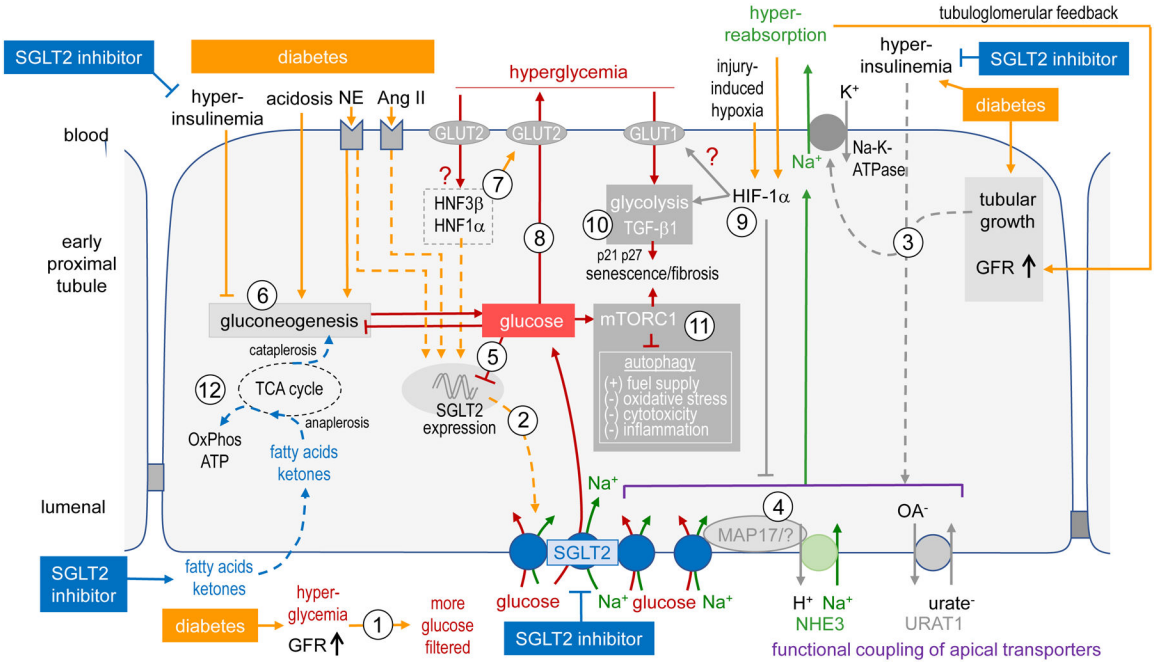

Figure 1: Cellular processes in the early proximal tubule linked to SGLT2 and its inhibition.

Hyperglycemia enhances filtered glucose and, via SGLT2, the reabsorption of glucose and Na^+ (1). Diabetes can increase SGLT2 expression (2) through tubular growth, angiotensin II (Ang II), sympathetic tone (norepinephrine, NE), and HNF-1α, which may respond to basolateral hyperglycemia sensed by GLUT2. Hyperinsulinemia and tubular growth upregulate proximal tubular transport systems, including SGLT2, NHE3, URAT1, and Na-K-ATPase (3). The apical transporters may be functionally coupled via scaffolding proteins, such as MAP17 (4). The resulting proximal tubular Na^+ retention enhances the GFR via tubuloglomerular feedback, which by increasing brush border torque can further increase transporter density in the luminal membrane. Intracellular glucose may feed back on SGLT2 upregulation (5). Diabetes, in part due to acidosis or NE, can enhance gluconeogenesis (6). Gluconeogenesis can be inhibited by tubular injury, hyperinsulinemia, and enhanced glucose uptake via SGLT2 (6). HNF-1α and HNF-3β upregulate GLUT2 (7) and thereby the basolateral exit of glucose and maintain hyperglycemia (8). Hypoxia due to diabetes-induced hyperreabsorption or kidney injury can induce HIF-1α, which enhances basolateral glucose uptake via GLUT1, induces a metabolic shift to glycolysis, and limits apical hyperreabsorption (9). Induction of TGF-β1 and tubular growth may be particularly sensitive to basolateral glucose uptake via GLUT1 (10). Hyperinsulinemia and excessive glucose stimulate mTORC1 and attenuate autophagy (11). TGF-β1 enhances cyclin-dependent kinase inhibitors p21 and p27 and together with mTORC1 activation promotes tubular senescence, which is linked to inflammation and fibrosis. SGLT2 inhibition enhances kidney delivery of fatty acids and ketone bodies and attenuates the deleterious effects linked to hyperinsulinemia, excessive intracellular glucose and hyperreabsorption. SGLT2 inhibition can enhance gluconeogenesis (e.g., by lowering hyperinsulinemia or cytosolic glucose). Gluconeogenesis enhances removal of intermediates from TCA cycle (cataplerosis) thereby facilitating the feeding of fatty acids and ketone bodies into the TCA cycle (anaplerosis), and enhancing oxidative phosphorylation (OxPhos) and ATP generation (12). Abbreviations:

GFR, glomerular filtration rate; GLUT, facilitative glucose transporter; HIF-1α, hypoxia-inducible factor 1 alpha; HNF, hepatic nuclear factor; MAP17, 17-kDa membrane-associated protein; NHE3, Na-H-exchanger 3; OA, organic anion; TGF-β1, transforming growth factor β1; URAT1, urate transporter 1.

Adapted from Vallon V, Nakagawa T. Renal Tubular Handling of Glucose and Fructose in Health and Disease. Compr Physiol. 2021;12(1):2995–3044.

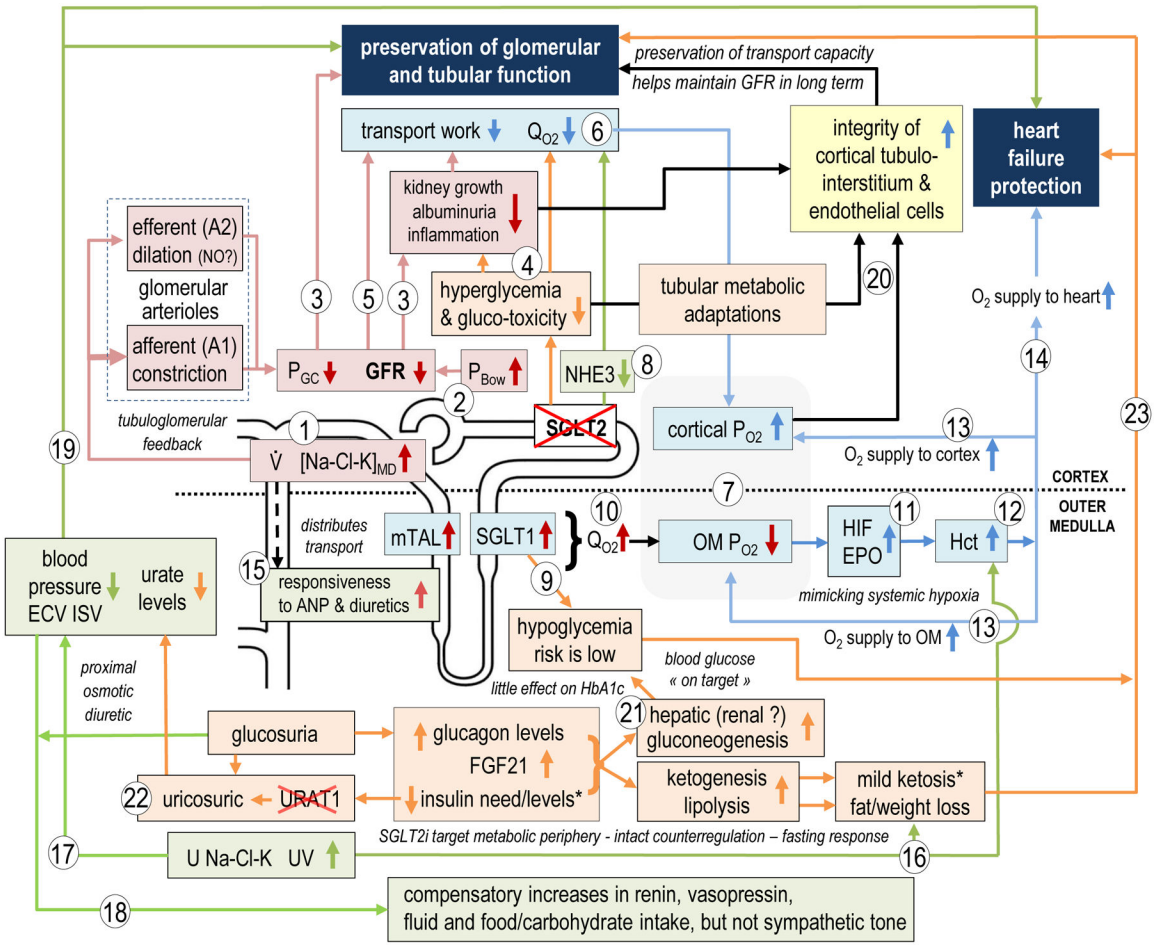

Figure 2: Kidney protective mechanisms of SGLT2 inhibition.

SGLT2 inhibition reduces the reabsorption of glucose and Na^+ in the early proximal tubule. This increases the delivery of NaCl and K ($[Na\text{-}Cl\text{-}K]_{MD}$) and fluid (V) to the macula densa, which lowers glomerular filtration rate (GFR) through the physiology of tubulo-glomerular feedback (TGF)(1) and by increasing hydrostatic pressure in Bowman's space (P_{Bow})(2). The TGF lowers GFR primarily by afferent arteriole constriction (via adenosine A1 receptor) but also by efferent arteriole dilation (via adenosine A2 receptor), which both reduce glomerular capillary pressure (P_{GC}). Lowering P_{GC} & GFR (3) and hyperglycemia (4) protects glomerular and tubular function. This includes lessening physical stress and filtration of albumin and other tubule-toxic compounds, tubular growth, and inflammation. Lowering GFR reduces tubular transport work (5), thereby lowering cortical oxygen demand (Q_{O2})(6) and increasing cortical oxygen availability (P_{O2})(7). Tubular transport work and toxicity are also reduced by lowering hyperglycemia and cellular SGLT2 blockade, which is also linked to inhibition of Na-H-exchanger NHE3 (8). SGLT2 inhibition shifts glucose reabsorption to downstream SGLT1, which limits glucosuria and hypoglycemia risk (9). Shifting glucose and Na^+ reabsorption to SGLT1 and medullary thick ascending limb (mTAL) increases Q_{O2} (10) and lowers P_{O2} in the outer medulla (OM)(7). which may activate hypoxia-inducible factor (HIF) and enhance erythropoietin (EPO) release (11). The resulting increase in hematocrit (Hct)(12) improves O_2 delivery to kidney medulla

and cortex (13) and other organs (14). More delivery of NaCl and fluid downstream of early proximal tubule may facilitate responsiveness to atrial natriuretic peptide (ANP) and diuretics (15). The diuretic effect of SGLT2 inhibition further increases Hct (16) and reduces extracellular (ECV) and interstitial (ISV) volume and blood pressure (17). These effects are evident by compensatory upregulation of renin and vasopressin levels (18), and can help protect the failing kidney and heart (19). The increased cortical oxygen availability together with lesser tubular stress promotes the integrity of the tubular and endothelial system and preserves higher tubular transport capacity and GFR in the long-term (20). The glucosuric effect lowers therapeutic and/or endogenous insulin levels and increases glucagon & FGF21 (21). This induces compensatory lipolysis, ketogenesis and gluconeogenesis. SGLT2 inhibitors are uricosuric; potentially involving URAT1 inhibition and their glucosuric and insulin-lowering effect (22). These metabolic adaptations reduce urate levels, the hypoglycemia risk, and body and organ fat mass, which together with the resulting mild ketosis have the potential to further protect the kidney and heart (19)(23). NO, nitric oxide; UNaClV, urinary salt excretion; UV, urinary flow rate.

Adapted from Vallon V. Glucose transporters in the kidney in health and disease. Pflugers Arch. 2020 Sep;472(9):1345–1370.