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REVIEW ARTICLE

Can SGLT2 Inhibitors Cause Acute Renal Failure? Plausible Role for Altered Glomerular Hemodynamics and Medullary Hypoxia

Auryan Szalat[1] · Amichai Perlman[1] · Mordechai Muszkat[1] · Mogher Khamaisi[2] · Zaid Abassi[3,4] · Samuel N. Heyman[1]

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Abstract Sodium–glucose co-transporter-2 inhibitors (SGLT2i) provide outstanding long-term cardiovascular and renal protection in high-risk patients with type 2 diabetes mellitus. Yet, despite encouraging renal safety outcomes reported in the EMPA-REG study, scattered reports suggest that there might be a risk for acute kidney injury (AKI), which may occasionally be fatal or might require renal replacement therapy. Reduced trans-glomerular pressure with a modest decline in kidney function, an inherent characteristic of SGLT2i therapy, conceivably forms the basis for the long-term renal protection, resembling agents that block the renin–angiotensin–aldosterone (RAAS) axis. Yet, a major decline in kidney function occasionally occurs, often associated with an acute illness or with specific co-administered medications. SGLT2i may lead to AKI by (a) effective volume depletion, due to excessive diuresis, particularly in hemodynamically unstable and volume-depleted patients; (b) excessive decline in trans-glomerular pressure, specifically in patients on RAAS blockade; and (c) induction of renal medullary hypoxic injury, related to enhanced distal tubular transport, especially with concomitant use of agents impairing medullary oxygenation, such as non-steroidal anti-inflammatory drugs and radiocontrast agents. The risk of developing renal impairment with SGLT2i and the role of these suggested mechanisms are yet to be defined, as there are conflicting data and inconsistent reporting with the various agents currently in use.

Key Points

Treatment with sodium–glucose co-transporter-2 inhibitors (SGLT2i) may lead to clinically significant acute kidney injury (AKI).

Mechanisms that possibly lead to SGLT2i-related AKI principally include dehydration, altered glomerular hemodynamics, and hypoxic medullary injury.

Caution is warranted regarding the hydration status of patients on SGLT2i, and with other clinical and pharmaceutical factors that affect glomerular hemodynamics or medullary oxygenation.

1 Introduction

The development of specific sodium–glucose co-transporter (SGLT)-2 (SGLT2) inhibitors (SGLT2i), such as canagliflozin, empagliflozin, and dapagliflozin, provides an

Auryan Szalat and Amichai Perlman contributed equally to the construction of the manuscript.

✉ Samuel N. Heyman
Samuel.heyman@mail.huji.ac.il

[1] Department of Medicine, Hadassah Hebrew University Hospital, Mt. Scopus, P.O. Box 24035, 91240 Jerusalem, Israel

[2] Department of Internal Medicine, Rambam Medical Center, Haifa, Israel

[3] Department of Physiology and Systems Biology, The Ruth and Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

[4] Department of Laboratory Medicine, Rambam Health Campus, Haifa, Israel

outstanding breakthrough in the management of type 2 diabetes mellitus (T2DM) as they substantially improve survival and prevent co-morbidities [1, 2]. The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) study has clearly shown that in addition to a better control of diabetes, empagliflozin markedly reduces the incidence of cardiovascular morbidity and mortality, supplemented with weight loss, natriuresis, and blood pressure reduction [3]. A comparable favorable cardiovascular outcome has been recently reported also with canagliflozin in the CANVAS (Canagliflozin Cardiovascular Assessment Study) trial, conducted in patients with high cardiovascular risk [4]. Further analysis of the EMPA-REG cohort revealed renal protection as well over 4 years of follow-up in patients with T2DM. Despite an early reduction in the glomerular filtration rate (GFR) in patients on empagliflozin, preservation of GFR was noted in the long run, as opposed to a gradual progressive decline in GFR in untreated controls [5]. Moreover, the incidence of pre-specified composite renal endpoints (defined as a doubling of the serum creatinine level, the initiation of renal replacement therapy, or death from renal disease) was halved in the empagliflozin groups, as compared with patients treated with placebo. The superiority of empagliflozin over placebo regarding renal outcomes was noted for all individual parameters included in the composite endpoint, as well as with the progression to macroalbuminuria. Renal outcome in the CANVAS study was also favorable, with attenuation of proteinuria and a significant decline in a composite endpoint identical to the one used in EMPA-REG study [4]. Renal protection with SGLT2i could be indirect, through modifications of cardiovascular risk factors, such as the correction of hyperglycemia and blood pressure reduction. Yet, improved renal outcomes conceivably reflect reduced trans-glomerular hydraulic pressure [6], manifested by an early 5% decline on the average in GFR upon initiation of treatment [5].

This modest decline in GFR, an inherent reversible feature of SGLT2i, has apparently been considered clinically insignificant, as the incidence of acute kidney injury (AKI) in patients on empagliflozin in the EMPA-REG study even declined beyond 18 months of randomization as compared with controls [4]. Treatment with SGLT2i has justly been considered recently to be a major advance in the attenuation or even prevention of diabetic nephropathy [1, 7], the major cause of end-stage kidney disease in developed countries [8]. Importantly, in both the EMPA-REG and CANVAS studies, SGLT2i were not associated with a risk of developing AKI [4, 5], and there was even a trend for attenuation of this risk with empagliflozin, starting 18 months after the initiation of therapy [5]. Yet, increasing numbers of reports of patients on SGLT2i who developed AKI, some requiring hospitalization and dialysis, raise concern regarding the safety of these medications under particular clinical settings, such as in the set-up of volume depletion or concomitant inhibition of the renin–angiotensin–aldosterone (RAAS) axis [9, 10].

In this report we review the impact of SGLT2i renal physiology and propose a consequent theoretic potential of these agents to exert substantial renal dysfunction and even damage. We conclude by presenting the current conflicting clinical data regarding renal safety of SGLT2i.

2 Sodium–Glucose Co-Transporter-2 Inhibitors (SGLT2i) Alter Renal Physiology

Normally, renal proximal tubules reabsorb all the glucose filtered through the glomeruli principally by two sodium-glucose linked co-transport systems on the apical membrane: SGLT2, located in the proximal segments (S1, S2) of the proximal convoluted tubules (PT); and SGLT1, expressed in the distal straight PT segment (S3). Glut1 and Glut2, located at the basolateral membrane, complete the glucose transport across the tubular cells into the blood stream (Fig. 1). SGLT1 and SGLT2, members of the *SLC5A* gene family, differ in their sodium/glucose co-transport ratio: 2/1 for SGLT1 and 1/1 for SGLT2. Glucose transport by SGLT2 accounts for over 90–97% of total glucose reabsorption along the nephron, the remaining fraction being uptaken by SGLT1 [11, 12]. Overall, some 180 g of filtered glucose are absorbed daily by these transport systems in non-diabetic individuals. Renal homeostasis in diabetes is altered by rising plasma glucose and increasing amounts of glucose filtered across the glomeruli. Glycosuria appears as the amount of filtered glucose exceeds the tubular maximal reuptake threshold, which is shifted upwards in diabetics. Indeed, glucose uptake by the PT substantially increases in the diabetic kidney in a maladaptive mechanism that helps maintain hyperglycemia [13], though there are conflicting data regarding the expression of glucose transporters in humans, ranging from selective upregulation of SGLT2 [14] to reduced expression of both SGLT1 and SGLT2 [15]. The increase in sodium glucose-coupled reuptake in the PT reduces delivery of sodium and chloride to the macula densa, leading to deactivation of the tubuloglomerular feedback mechanism (TGF), with a reduction in afferent arteriolar tone and increased GFR [16]. Overall, renal hyperfiltration coupled with enhanced tubular transport are the principal players in the generation of diabetic nephropathy and its progression to chronic kidney disease (CKD) [17].

As shown in Fig. 2, SGLT2i break this loop by enhancing sodium and chloride delivery to the distal

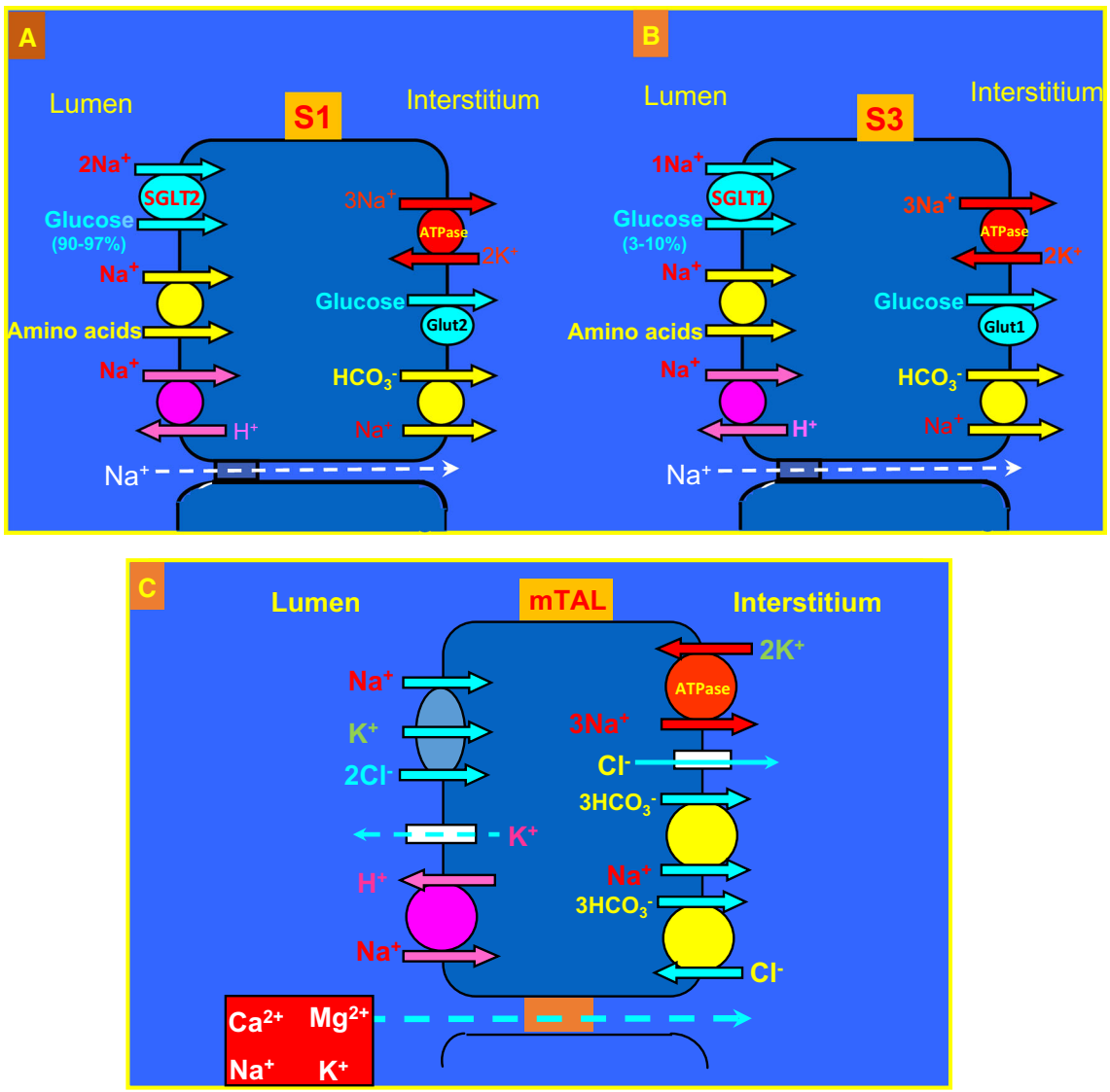

Fig. 1 Schematic illustration of major transport systems: **a** in proximal convoluted tubules (S1 and S2 segments); **b** in the distal S2 and straight segment (S3) of the proximal tubule; and **c** in medullary thick ascending limbs. Importantly, the proximal and distal segments of the proximal tubule express on their apical membrane different isoforms of sodium–glucose co-transporter (SGLT): SGLT2 in the proximal segments and SGLT2 in the more distal segments. GLUT isoforms on the basolateral membrane facilitate trans-cellular glucose transport into the blood stream. *mTAL* medullary thick ascending limbs

nephron, reactivating TGF through the macula densa. This leads to restoration of afferent arteriolar tone, reducing trans-glomerular pressure and hyperfiltration. Increased downstream solute delivery to S3 segments and to the distal nephron is associated with enhanced tubular transport of glucose (in S3 segments by SGLT1) and sodium [particularly by S3 segments and by medullary thick ascending limbs (mTALs)]. These adjustments to some extent blunt the action of SGLT2i, yet only partially, leading to a net increase in urine volume and glucose and sodium excretion [1].

Activation of the TGF is believed to be the major mechanism by which SGLT2i exert kidney protection in the long run [18], but with the price of an early reduction of GFR by some 5%, on average [5, 6]. Larger declines in GFR might be regarded as worrisome, and discriminating between a favorable decline in GFR and an exaggerated response invoked by harmful mechanisms might be difficult.

In addition to these mechanisms of readjustment of renal hemodynamics by SGLT2i, there are additional direct renoprotective effects of these agents on the attenuation of renal metabolic derangements and by reducing lipid accumulation and inflammation [14]. Reduced albuminuria, associated with a decline in net glomerular filtration pressure [5], might also be involved in attenuating these

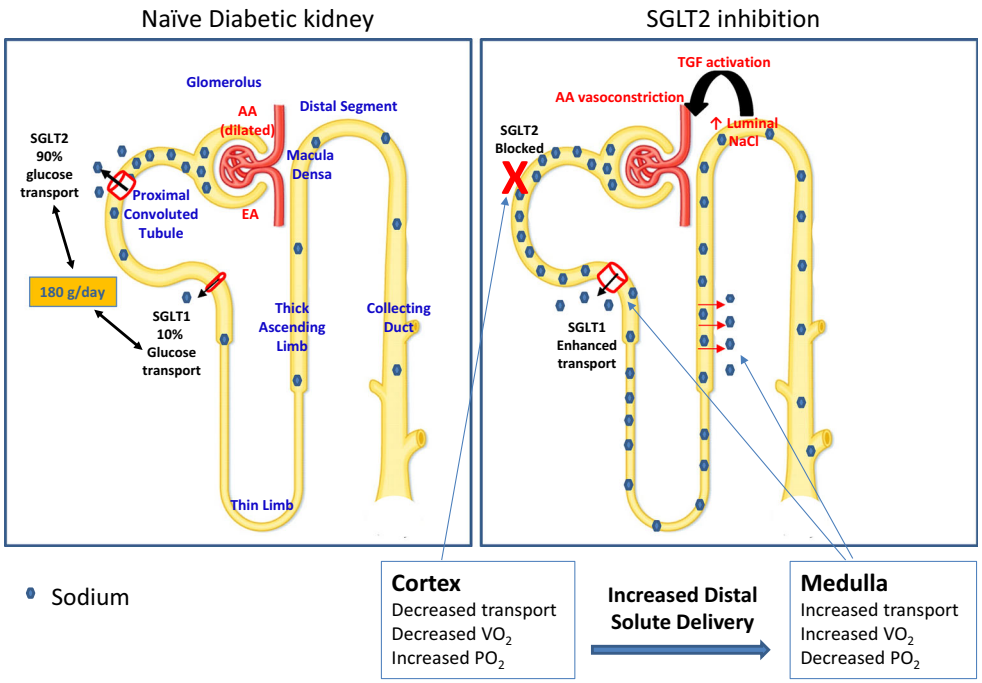

Fig. 2 The impact of SGLT2 inhibition on sodium transport and oxygen consumption along the nephron: in the naïve diabetic kidney sodium and chloride concentration at the macula densa diminishes because of intense upstream sodium reabsorption, along with glucose by SGLT and GLUT transporters. Consequently, the tubuloglomerular feedback mechanism is inhibited, leading to afferent arteriolar vasodilation, with enhanced trans-glomerular hydraulic pressure and glomerular filtration. Oxygen consumption for transport is enhanced in proximal and distal tubular segments. With sodium–glucose co-transporter (SGLT)-2 inhibition a prominent portion of sodium reabsorption in the proximal convoluted tubule is shifted to more distal tubular segments, namely by upregulated SGLT1 in S3 segments and by medullary thick ascending limbs. Yet, overall renal conservation of sodium and glucose declines, with consequent glycosuria and natriuresis. Note that increased luminal sodium and chloride concentrations in the macula densa activate tubuloglomerular feedback, reversing afferent arteriolar vasodilation, hence reducing trans-glomerular filtration and the glomerular filtration rate. The shift of sodium transport (blue hexagons) from cortical to outer medullary nephron segments reduces cortical transport and oxygen expenditure (VO_2) with increased cortical partial pressure of oxygen (pO_2), whereas outer medullary VO_2 increases and medullary pO_2 declines. *AA* afferent arteriolar, *TGF* tubuloglomerular feedback

metabolic derangements and the progression to CKD [19]. In the following sections, however, we restrict our discussion to the impact of SGLT2i on the renal microcirculation and renal oxygen expenditure, as well as their potential deleterious effects on renal function and integrity.

3 SGLT2i Alter Trans-Glomerular Pressure

As discussed earlier, and as is documented in patients [20], reduced trans-glomerular hydraulic pressure with a modest decline in kidney function is an inherent characteristic of SGLT2i, plausibly contributing to their renal protection in the long run. SGLT2i may lead to AKI by reducing trans-glomerular pressure more than desired. This can result from depletion of renal perfusion due to reduced effective blood volume, disruption of the balanced tone of afferent and efferent arterioles, or their combination.

3.1 Reduced Effective Blood Volume

Animal studies disclose that non-selective SGLT inhibition is associated with marked polyuria, glycosuria, and natriuresis [21]. This is also the case with the administration of selective SGLT2i, despite some attenuating impact of the upregulated SGLT1. It is possible that polyuria and natriuresis contribute to the marked cardiovascular protection, noted very early following the initiation of treatment in high-risk patients [3]. In fact, SGLT2i might be regarded as diuretics, with some 200–600 mL excess of urine volume per day and a 2–5 mmHg drop in systolic blood pressure [22]. Thus, patients on diuretics, frail elderly individuals with limited access to fluids, or patients with congestive heart failure (CHF) might be especially susceptible to clinically significant effective volume depletion and consequent pre-renal failure [23]. This possibility per se can easily be overlooked if patients are not checked for

orthostatic hypotension, and may manifest solely as a gradual increase in plasma creatinine. Furthermore, SGLT2i-related negative fluid balance may become apparent with coexisting illness leading to excessive fluid losses such as diarrhea, or to diminished fluid intake.

3.2 Altered Glomerular Hemodynamics

Volume depletion stimulates sympathetic activity and the release of vasopressin and turns on the RAAS axis, leading to reduced renal blood flow (RBF). Furthermore, diabetic patients on SGLT2i are most often co-administered RAAS blockers as the first-choice antihypertensive therapy [24] or to attenuate proteinuria, principally with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). These agents diminish trans-glomerular hydraulic pressure by predominant efferent arteriolar vasodilation, especially in glomeruli with hyperfiltration and increased trans-capillary pressure [18, 25]. Thus, it is conceivable that the combined impact of SGLT2i and RAAS blockade might lead to an exaggerated reduction in trans-glomerular hydraulic pressure and GFR due to the concomitant reversal of afferent arteriolar vasodilation by SGLT2i and the predominant efferent arteriolar vasodilation produced by RAAS blockade. Coexisting effective volume depletion due to excessive fluid loss may further intensify GFR reduction in this scenario, leading to profound pre-renal AKI.

4 SGLT2i Intensify Renal Medullary Hypoxia

Pre-renal AKI, devoid of renal structural damage, is considered mild and easily reversible. Therefore, occasional reports of profound and protracted renal functional impairment with SGLT2i, occasionally requiring renal replacement therapy [9], conceivably suggest that renal structural damage may develop as well. Few lines of evidence, detailed in Sect. 4.1, led us to hypothesize that treatment with SGLT2i bears the potential to predispose to renal hypoxic injury, most likely in the form of acute tubular necrosis (ATN) [10]. In Sect. 4.1, basic concepts regarding renal parenchymal oxygenation and the pathogenesis of renal hypoxic ATN are summarized. In these perspectives, SGLT2i might be added to a list of 'nephrotoxic' agents that in fact are not true tubulotoxic mediators but exert renal injury through the induction of hypoxic medullary injury.

4.1 Hypoxic Medullary Injury: Physiologic Background

Global renal hypoxia with acute cortical necrosis develops very rarely, usually in the setup of profound and protracted post-partum shock. In clinical practice, however, hypoxic ATN does not require profound and protracted shock to develop, and is most often morphologically subtle, with rare focal tubular injury, mostly within the renal outer medulla [26, 27]. This type of injury has been recognized in autopsies performed during the pre-dialysis era in World War II in patients dying of AKI [28, 29], but its recognition nowadays is undervalued, as patients usually recover and rarely undergo biopsies. Furthermore, if biopsies are undertaken, they are usually performed too late, at the maintenance and recovery stages of AKI [30], and a deeply seated focal injury pattern is only rarely captured by random small-volume biopsies [27]. This is a principal reason that the term 'ATN' has been replaced by 'AKI', underlining the absence of tubular injury in biopsy specimens. The clinician may consider hypoxic AKI in the likely clinical setup and in the presence of impaired distal tubular function (declining urine osmolality and fractional tubular sodium reabsorption), with urine sediment containing tubular casts, or with increasing levels of specific urinary biomarkers, indicating tubular injury [31].

Brezis and colleagues [26, 32] conceived the concept of the renal oxygenation paradox in the mid-1980s, underscoring that within the well-oxygenated kidney the renal medulla functions normally within a profoundly hypoxic environment. Blood and oxygen supply to the kidney surpasses all other organs, and is five times higher than blood flow to the myocardium. At the same time, oxygen extraction by the kidney is only 10% of the total of renal oxygen supply, as opposed to 65% oxygen extraction by the heart. These figures illustrate that most of the renal blood supply, being used for the filtration process, by far exceeds its metabolic requirements. Paradoxically, as illustrated in Fig. 3, whereas the renal cortex receives an oxygen supply far beyond its metabolic needs, the renal medulla receives less than 10% of the total RBF and likely extracts 79% of the delivered oxygen for intense transport activity [26]. Consequently, renal parenchymal pO_2 (partial pressure of oxygen) normally declines at the cortico-medullary junction and reaches values as low as 30 mmHg in the outer medulla. Medullary hypoxia is the price the mammalian kidney pays for the ability to concentrate urine, as low regional blood flow is required for the formation of the cortico-medullay osmolar gradient [26, 32].

As shown in Table 1 and reviewed in Heyman et al. [33], outer medullary oxygen balance is governed on the one hand by structural and functional alterations in the regional microcirculation (originating from vasa recta, emerging from deep juxtaglomerular nephrons), and on the other hand by the extent of regional oxygen consumption for tubular transport, particularly by mTALs and S3 segments. Regional microcirculation might be injured and depleted in CKD. Furthermore, it may be influenced by the

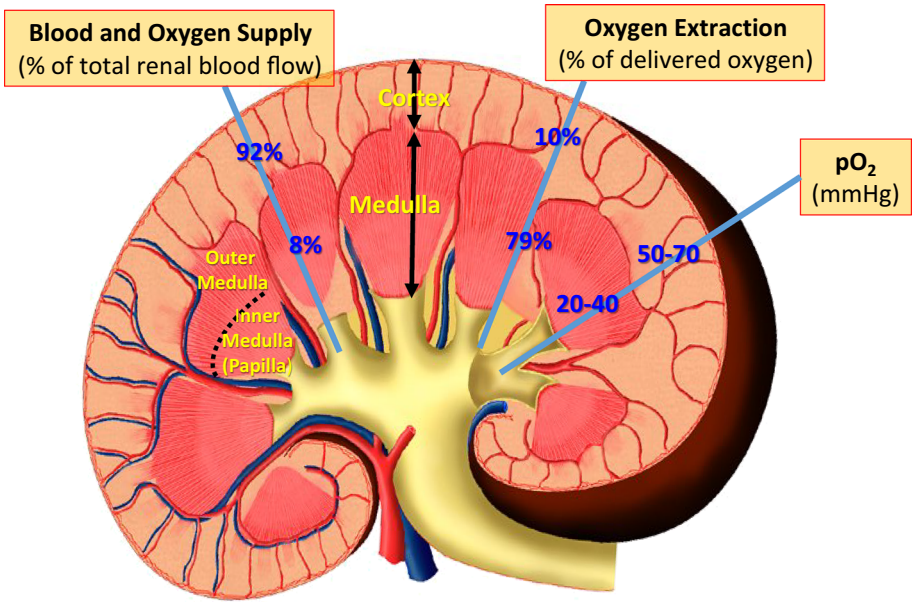

Fig. 3 Renal oxygen supply and demand. The kidneys receive almost a quarter of the cardiac output for the filtration process, and whole-organ oxygen consumption is very low. However, blood and oxygen supply to the renal medulla is hardly sufficient for the regional high oxygen consumption for transport activity, reflected by near-maximal oxygen extraction. Consequently, hypoxia normally exists at the renal medulla and the oxygen reserve at this region is negligible [26]. Highly efficient mechanisms maintain oxygen levels at this vulnerable region in the normal kidney by matching local oxygen supply and demand. These mechanisms are altered in the diabetic kidney resulting in intensified hypoxia (see text). pO_2 partial pressure of oxygen

regulation of total RBF distribution between cortical and juxtamedullary glomeruli and by the control of pericyte contraction along vasa recta. Oxygen consumption for tubular transport in the outer medulla is affected by the amount of solute delivered to distal tubular segments (governed by GFR and transport activity in proximal tubular segments), and is also directly regulated by complex physiologic systems, including prostaglandins, nitric oxide, and adenosine, which maintain medullary oxygen sufficiency by strict matching of regional oxygen delivery and consumption for tubular transport. They act through suppression of distal tubular transport and oxygen requirement, and by enhancement of medullary blood flow through vasa recta. Some of these mechanisms in charge of the maintenance of medullary oxygen sufficiency are altered by oxygen free radicals and under conditions known to predispose to hypoxic AKI, such as CKD, diabetes, or aging. Nevertheless, in most circumstances they are highly effective at maintaining medullary oxygenation and in the prevention of medullary hypoxic injury caused by trivial daily changes in the hydration status and renal solute loads and under additional physiologic alterations [32–34].

Acute severe medullary hypoxia leads to tubular morphologic injury, mostly involving mTALs and S3 segments. Damage may range from reversible changes, such as mitochondrial swelling, through to programmed cell death (apoptosis) or frank tubular cell disruption [27, 35]. Hypoxia also leads to hypoxia adaptive responses, mediated to a large extent through stabilization of hypoxia-inducible factors (HIF), key regulators of cellular hypoxia adaptive responses. HIF-mediated induction or suppression of numerous genes may trigger pro-fibrotic processes that participate in the progress of CKD, but on the other hand may confer tolerance to acute hypoxic and toxic stresses and attenuate the development of AKI [36].

4.2 Renal Hypoxia in Diabetes

Diabetes is characterized by globally reduced parenchymal oxygenation with an intensification of physiologic medullary hypoxia. This has been clearly documented in vivo in rodents by oxygen microelectrodes inserted into the renal parenchyma [37]—non-invasively using blood oxygenation level-dependent magnetic resonance imaging (BOLD MRI)—assessing the amount and distribution of deoxygenated hemoglobin in the renal parenchyma [38], and by the detection of pimonidazole adducts and HIF stabilization in the renal medulla [39]. Intensification of renal medullary hypoxia in diabetes is related at early disease stages to enhanced GFR, increased tubular mass, and augmented solute delivery to S3 and to the distal nephron [40]. Excess solute delivery to the distal nephron leads to increased transport burden and oxygen requirement. Furthermore, reactive oxygen species (ROS) in the diabetic kidney lead to dis-inhibition of sodium/potassium (Na/K)

Table 1 Determinants of medullary oxygen balance: major factors affecting renal medullary oxygen consumption and expenditure for tubular transport activity

Improved medullary oxygenation	Reduced medullary oxygenation
Increased regional blood/oxygen supply	*Decreased regional blood/oxygen supply*
Prostaglandins (PGE2, PGI2)	Altered cyclo-oxygenase (NSAIDs, aging)
Nitric oxide	Altered nitrovasodilation (D, dyslipidemia, and other causes for enhanced ROS formation)
Adenosine (mediated by adenosine A_2 receptors)[a]	Hypotension with mean BP < 65 mmHg[b]
Endothelin (mediated by endothelin ETB receptors)[a]	Profound decline in total or medullary blood flow other than hypotension (endogenous or exogenous vasoconstrictors)
Angiotensin II (mediated by AT_2 receptors)[a]	Increased interstitial pressure (radiocontrast agents, urine outflow obstruction)
	Rarefaction of capillary meshwork in CKD (D)
	Anemia
Decreased medullary transport activity	*Increased medullary transport activity*
Pre-renal failure (S-mediated and other causes of dehydration, hypotension but with BP > 65 mmHg)[b]	Enhanced GFR or single-nephron GFR (D, high-protein diet, CKD with reduced number of nephrons, post-nephrectomy compensatory hypertrophy of remnant kidney, pregnancy)
Declining GFR due to other causes (S and other factors activating TGF, including AKI, RAAS blockade)	Reduced transport activity in proximal tubular segments (S)
Increased proximal tubular reabsorption (reduced GFR, dehydration)	Other causes of enhanced solute delivery to distal nephron segments (D, mannitol, radiocontrast agents)
Loop diuretics[c]	Dis-inhibition of Na/K/ATPase in mTALs (ROS, NSAIDs)

Plausible impacts of diabetes and sodium–glucose co-transporter-2 inhibitors (SGLT2i) are highlighted. The net effect of both diabetes and SGLT2i is a reduction in medullary partial pressure of oxygen by combined decline in regional blood flow and enhanced tubular transport and oxygen consumption

AKI acute kidney injury, *BP* blood pressure, *CKD* chronic kidney disease, *D* diabetes, *GFR* glomerular filtration rate, *mTALs* medullary thick ascending limbs, *Na/K* sodium/potassium, *NSAIDs* non-steroidal anti-inflammatory inhibitors, *RAAS* renin–angiotensin–aldosterone, *ROS* reactive oxygen species, *S* sodium–glucose co-transporter-2 inhibitors (SGLT2i), *TGF* tubuloglomerular feedback mechanism

[a]The intra-renal distribution of receptor subtypes governs the response of local microcirculation and oxygenation. In that way, adenosine, endothelin-1 and angiotensin II exert renal cortical vasoconstriction through adenosine A_1, endothelin ETA and angiotensin II AT_1 receptors, respectively, while they preserve or augment medullary blood flow by stimulating local adenosine A_2, endothelin ETB, and angiotensin II AT_2 receptors, respectively [83, 89, 90]. Thus, the renal medulla is physiologically protected by the most potent vasoconstrictors by local vasodilation, combined with reduced GFR

[b]The degree of reduced renal perfusion pressure governs the outcome of medullary oxygenation: above 65 mmHg regional blood flow is grossly maintained but GFR (hence transport activity) markedly diminishes, resulting in improved medullary oxygenation [69]. If mean perfusion pressure further declines, medullary blood flow and oxygenation falls

[c]Interestingly, medullary oxygenation markedly increases with loop diuretics despite a substantial fall in regional blood flow [54], underscoring the predominant impact of transport activity on medullary oxygenation

ATPase activity in tubular basolateral membranes (resulting in augmented tubular transport and oxygen consumption) and to some decline in medullary blood flow. This concept has been supported in experimental settings, showing improved medullary oxygenation and medullary blood flow, as well as attenuation of tubular oxygen consumption with the chronic administration of antioxidants [37]. Finally, advanced diabetes-associated CKD is characterized by tubulo-interstitial fibrosis and compromised microcirculation with rarefaction of peritubular capillaries, leading to a feed-forward loop of renal hypoxia and profibrotic changes with progressive CKD [41]. Importantly, the diabetic kidney is predisposed to AKI [42], despite the induction of HIF-mediated cellular hypoxia-adaptive mechanisms [39], and likely reflects enhanced ROS formation and disruption of many of the systems in charge of maintaining adequate oxygenation balance. Furthermore, maladaptive hypoxia-driven responses in the diabetic kidney likely contribute to the progression of CKD following AKI [36, 43].

4.3 Disrupted Medullary Oxygenation and Drug-Induced Hypoxic Acute Tubular Necrosis

'True' tubulotoxic agents are up-taken by drug-specific nephron segments with particular drug transport systems, and cause a dose-dependent and predicted ATN by injuring cellular structures and disrupting vital cellular physiologic systems. Tubular segment specificity for drug toxicity is illustrated, for example, by aminoglycoside- and cis-

Table 2 Drugs affecting medullary oxygenation

Drug	Effect on regional oxygen supply	Effect on regional oxygen demand	Comments	References
Reducing medullary pO_2				
NSAIDs	↓	↑		[47]
Cyclosporine (ciclosporin)	↓	?↓	Reduced medullary oxygen consumption in part due to reduced GFR and solute load to the distal nephron, yet vasoconstriction and reduced oxygen supply prevails	[55]
Amphotericin	↓	↑		[56]
Radiocontrast media	↓	↑		[47]
Mannitol	?↓	↑		[47]
ANP	?	↑		[91]
SGLTi	?↓	↑	Medullary hypoxia has been documented with non-selective SGLTi. It is anticipated that with SGLT2i this effect might be even more pronounced because of enhanced transport by S3 segments, located at the outer medulla [40]	[21][b]
Increasing medullary pO_2				
Furosemide	↓	↓↓	Improved medullary oxygenation develops despite profound reduction in medullary blood flow, illustrating the major impact of reduced oxygen demand for tubular transport	[54]

ANP atrial natriuretic peptide, *GFR* glomerular filtration rate, *NSAIDs* non-steroidal anti-inflammatory drugs, *pO_2* partial pressure of oxygen, *SGLT2i* sodium–glucose co-transporter-2 inhibitors, *SGLTi* sodium–glucose co-transporter inhibitors, ↓ indicates decrease, ↑ indicates increase, ? indicates unknown

platinum-induced injury that characteristically involves convoluted PT and S3 PT segments, respectively. The major determinant influencing the risk of toxic AKI other than dosage is the rate of tubular cell uptake, markedly influenced by the hydration status and sodium balance, which governs the tubular intraluminal urine transit time and drug concentration and uptake [44]. By contrast, some drugs, erroneously classified as 'nephrotoxins', actually lead to AKI by the induction of severe medullary hypoxia and subsequent formation of oxygen free radicals [32]. Unlike classical nephrotoxins, AKI induced by these agents may be especially prominent in patients with co-morbidities predisposing to medullary hypoxia and hypoxic injury, whereas healthy individuals with intact mechanisms that maintain medullary oxygenation equilibrium are rather protected. For this reason, resembling clinical practice, clinically relevant animal models of hypoxic AKI are quite complex and require the induction of predisposing states, either pharmacological [such as the inactivation of nitric oxide synthase (NOS)] or conditional (such as the reduction of renal mass, induction of CHF, diabetes, CKD, urine outflow obstruction, etc.) [35, 44, 45]. In these models outer medullary pO_2 levels as low as 8–10 mmHg are recorded, and in addition to papillary tip necrosis tubular injury principally involves mTALs and S3 segments, which are characterized by intense oxygen demand for transport activity.

Non-steroidal anti-inflammatory drugs (NSAIDs) represent medications that may lead to AKI through the induction of medullary hypoxic injury (Table 2). NSAIDs reduce the GFR by altering glomerular hemodynamics and lowering trans-glomerular pressure [46]. This would lead to improved medullary oxygenation, as solute delivery to the distal nephron decreases. Yet, medullary oxygenation declines with NSAIDs [47, 48], reflecting a selective reduction in medullary blood flow, combined with dis-inhibition of Na/K/ATPase in mTALs [49]. Conceivably, NSAID-associated AKI involves medullary hypoxic injury, particularly in patients predisposed to altered medullary oxygenation. For instance, experimental mTAL hypoxic injury by NSAIDs substantially increased in rats with CHF concomitantly given NOS inhibitors [50], mimicking clinical conditions with altered endothelial NOS (eNOS) activity, such as dyslipidemia or diabetes.

In the same manner, radiologic contrast media exert substantial medullary hypoxia as they compromise medullary blood flow and transiently increase tubular transport and oxygen consumption [47, 51]. These agents may lead to hypoxic medullary injury, in particular with other co-insults that dis-regulate medullary oxygen balance. The already hypoxic diabetic kidney is indeed predisposed to radiocontrast-induced nephropathy, as indicated by clinical studies and under experimental settings [34, 52, 53].

Likewise, as illustrated in Table 2, cyclosporine and mannitol also induce medullary hypoxia and hypoxic injury [54, 55], and some extrinsic and intrinsic nephrotoxins, such as amphotericin and myoglobin, respectively, may act through combined direct tubulotoxicity and hypoxia [56, 57]. By contrast, loop diuretics that inhibit ion transport and oxygen consumption in mTALs attenuate medullary hypoxia [54] and hypoxic medullary injury [58]. In fact, early studies suggesting increased risk for radiocontrast nephropathy with loop diuretics likely reflected insufficient volume replacement [59, 60], and forced diuresis combined with loop diuretics was found to substantially decrease the likelihood of radiocontrast nephropathy in high-risk patients [61].

5 SGLT2i Alter the Renal Oxygenation Profile

The impact of SGLT2i on renal oxygenation is highly complex with often opposing trends that principally involve reducing GFR, translocation of tubular transport from proximal to distal segments, changes in transport efficiency (energy expenditure per transported ions), and shifts between trans-cellular and para-cellular fractions of solute reabsorption [40]. O'Neill et al. [21] studied the effect of phlorizin, a non-selective SGLT inhibitor on renal parenchymal oxygenation in diabetic and intact rats using Clark-type oxygen microelectrodes. They found that renal cortical pO_2, depressed in diabetic rats, normalized with phlorizin, likely as the result of reduced GFR and diminished cortical transport [40], resembling the impact of acetazolamide, an inhibitor of cortical carbonic anhydrase [54]. At the same time, outer medullary pO_2 significantly declined to levels as low as 22 mmHg both in diabetic and non-diabetic animals [21], conceivably reflecting enhanced oxygen consumption by mTALs, the consequence of increased solute delivery to distal nephron segments.

So far, comparable studies have not been conducted with selective SGLT2i. Using a mathematical model of transport shift from proximal to distal PT segments, Layton et al. [40] anticipated that enhanced transport by S3 segments would decrease medullary oxygenation. We have previously shown that S3 and mTALs, both located in the outer stripe of the outer medulla, compete with each other on the sparse regional oxygen supply [62]. Therefore, we anticipate that selective SGLT2i might more profoundly depress outer medullary oxygenation, since, in addition to augmented transport by mTALs, upregulated glucose/sodium transport by SGLT1 in S3 segments may further increase oxygen expenditure in the outer stripe of the outer medulla (Fig. 2). In other words, it is likely that enhanced transport and oxygen consumption by both tubular segments located at the same region might further substantially depress regional oxygenation.

Indeed, dapagliflozin administration resulted in enhanced HIF detection in intact kidneys of mice and in kidneys subjected to ischemia-reperfusion, suggesting enhanced hypoxia [63]. Interestingly, enhanced HIF expression was associated with reduced ischemia-reperfusion tubular injury, perhaps due to enhanced HIF-mediated hypoxia adaptive response [64]. However, caution is warranted regarding the significance of these findings, since HIF was upregulated by dapagliflozin ex vivo, and since the renal distribution of intensified HIF expression has not been specified.

Compelling evidence of a clinically significant SGLT2i-related medullary hypoxia comes from human studies showing increased hematocrit in patients treated with dapagliflozin for 12 weeks [65]. While diuresis-related hemoconcentration could account for this phenomenon, Lambers Heerspink et al. [65] further demonstrated reticulocytosis, as well as increased levels of circulating erythropoietin, suggesting there was also enhanced erythropoiesis. Erythropoietin, a HIF-2α target gene, is released from peritubular interstitial cells in the deep cortex, triggered by reduced ambient oxygenation [66]. It is therefore tempting to assume that SGLT2i reduce pO_2 in the deep cortex and outer medulla, stabilizing HIF-2α in these cells, hence promoting trans-activation of erythropoietin and leading to the observed reticulocytosis [67].

6 Additional Mechanisms that may Predispose to SGLT2i-Related Renal Impairment

Atherosclerotic disease of the renal arteries commonly develops in patients with long-standing diabetes [68]. It is likely that hypovolemia caused by SGLT2i might lead to global renal ischemia and acute or chronic progressive hypoxic injury in patients with critical renal artery stenosis, particularly if renal perfusion pressure drops below a mean pressure of about 65 mmHg [69].

SGLT2i may also lead to adverse renal effects via altered tubular metabolism. Enhanced glucose delivery to the S3 segment can locally induce aldose reductase with secondary generation of sorbitol and eventually fructose, with consequent generation of uric acid, leading to oxidative stress, inflammation, and tubular injury [70]. Furthermore, SGLT2i may enhance uricosuria via SLC2a9b-mediated glucose-uric acid exchange [71], with possible uric acid-induced tubulointerstitial damage [72].

7 Are SGLT2i Indeed Associated with Increased Risk for Acute Kidney Injury?

Since, as outlined in Sect. 3, reducing trans-glomerular hydraulic pressure and GFR is a fundamental inherent feature of SGLT2i, the risk of deteriorating kidney function has been assessed in all clinical trials with SGLT2i. A decline in GFR by about 2–6 mL/min/1.73 m^2 has been consistently noted following initiation of treatment, being a concern especially in patients with renal impairment at baseline [73–76].

Such a decline in GFR over time might vary between the different agents. A recent meta-analysis evaluated the physiological and metabolic effects reported in 34 randomized controlled trials of SGLT2i with $\geq$ 12 weeks of follow-up [77]. This analysis found that as a class, SGLTi slightly increased serum creatinine compared to placebo, and that this effect was driven primarily by results of studies with canagliflozin, as empagliflozin and dapagliflozin did not decrease GFR significantly as compared to placebo.

Importantly, most prospective clinical trials were not conducted specifically to assess renal risks, and therefore their design did not include indepth evaluation of the impact of concomitant medications or hydration status, and nor was the patients' urine evaluated for features of AKI, including checking for urinary sediment and biomarkers in patients with declining kidney function.

Therefore, a recent US Food and Drug Administration (FDA) Drug Safety Communication, reporting 101 cases of AKI in patients treated with SGLT2i [5] raises concern and deserves a special attention, as many of these patients required hospitalization and even renal replacement therapy. All patients were receiving dapagliflozin or canagliflozin, and it remains a matter of speculation whether the absence of reports with empagliflozin reflects improved safety or if there is a class effect and the absence of reports with empagliflozin results from a later introduction of this medication to the market than the two other SGLT2i. As pointed out by this communication, many patients had predisposing conditions, including age, CKD, CHF, effective blood volume depletion, or the concomitant use of diuretics, NSAIDs or agents blocking the RAAS. Some patients were evidently hypotensive and hypovolemic, underscoring a role for the diuretic properties of SGLT2i. In approximately half of the patients, AKI developed within the first month of treatment with SGLT2i, and in most cases renal functional impairment resolved upon cessation of this medication [5].

We have recently experienced a few cases of AKI that may have been linked to the initiation of treatment with SGLT2i, including empagliflozin, and further evaluated the adverse effects reported by the FDA. In a database comprising over 3,800,000 reports of drug-related adverse events, the proportion of patients with acute renal failure (ARF) associated with the use of SGLT2i was significantly greater than that of ARF among reported diabetic patients not receiving SGLT2i, with a relative reporting rate of 1.57 (Perlman et al. unpublished data). These findings are of course of limited value, and further prospective randomized studies in high-risk patients are needed. Meanwhile, retrospective analyses of available data provide some additional insight.

A meta-analysis of 48 RCTs of SGLT2i, published in 2013 [78], reported on the risk of renal adverse events with SGLT2i according to baseline renal function. This analysis disclosed that in patients with normal or mildly impaired renal function, only high doses of canagliflozin (300 mg) were associated with increased renal adverse events, while in patients with moderate renal failure the incidence of renal adverse events was increased by both canagliflozin and dapagliflozin [78].

A more recent meta-analysis evaluated the risk of composite renal outcome and of ARF in 58 and 53 placebo-controlled clinical trials, respectively [79]. This analysis disclosed a heterogeneous pattern. In the pooled pairwise comparisons of the SGLT2i and controls, both dapagliflozin and canagliflozin were significantly associated with increased risk for the composite renal events outcome [odds ratio (OR) 1.69 and 1.7, respectively], while empagliflozin seemed to be renoprotective (OR 0.62). As to the risk for developing ARF, both canagliflozin and dapagliflozin were associated with a tendency to increase the risk for ARF compared to control (OR 1.82 and 1.93, respectively); however, these results were based on a very small number of events (five and seven, respectively) and were not statistically significant. In contrast, empagliflozin was associated with a significant reduction in the risk of ARF (OR 0.72) [79], an effect largely driven by the results reported in the EMPA-REG study [5]. It is noteworthy, however, as opposed to the cited meta-analyses which showed a safety advantage for empagliflozin, that the recently published CANVAS trial illustrates that canagliflozin may also exert a positive impact on renal outcome, without a specific predisposition to AKI [4].

Further studies are therefore needed to confirm a possible difference between SGLT2i regarding renal safety. If empagliflozin will eventually be found to be safer, it may reflect diverse specificities to SGLT2 receptors between agents. Of note, SGLT2 specificity of empagliflozin is two- and tenfold higher than that of dapagliflozin and canagliflozin, respectively [80]. This might imply that altered glomerular hemodynamics, rather than intensified hypoxia, is the major mechanism involved in SGLT2i-associated

AKI, since a decline in outer medullary pO_2 is anticipated to be more pronounced with the more selective agent, as increased SGLT1-mediated transport is expected to intensify hypoxia in the outer stripe of the outer medulla [40]. In summary, current data are limited and further clinical studies, at this time underway, are needed to compare the safety of the different available medications regarding the risk of developing AKI.

8 Clinical Perspective

Identifying evolving ATN due to SGLT2i and distinguishing between this type of AKI and pre-renal failure may be difficult, as SGLT2i induce natriuresis and polyuria, with enhanced fractional sodium excretion. The differentiation between these two potential mechanisms is important in order to assess their individual contribution in affected patients and to initiate appropriate treatment. Clinical assessment of the hydration status helps identify volume depletion as a cause of pre-renal failure. Detection of tubular cell casts in the urinary sediment is highly specific and might be helpful in the recognition of ATN, though the sensitivity of this finding may be limited. Studies using urine biomarkers [31] may be helpful in prospectively assessing the true occurrence of hypoxic tubular injury in patients taking SGLT2i, and particularly in individual patients with declining kidney function. Animal studies may shed further light on the possible role of intensified hypoxia in SGLT2i-related AKI.

Until this issue is settled, we propose special care be taken regarding maintenance of hydration status, in order to reduce the risk of volume depletion in high-risk diabetic patients on SGLT2i. Furthermore, close monitoring of kidney function using serum creatinine or cystatin C is recommended, particularly during initiation of coadministration of SGLT2i and RAAS blockade. A progressive accelerate decline in estimated GFR (eGFR) following the initiation of SGLT2i treatment, beyond the anticipated 5–10% reduction, considered 'renoprotective', might reflect significant renal artery stenosis with the risk of developing global renal ischemic injury. Notably, changes in serum creatinine and extrapolated eGFR are delayed and inaccurate regarding real-time assessment of acutely declining GFR, especially in the diabetic patient. Alternative clinically applicable methods, such as monitoring changes in cystatin C or monitoring urine biomarkers for renal parenchymal injury are needed. Finally, with the possibility of hypoxic medullary injury in mind, it is prudent to suggest avoiding the concomitant administration SGLT2i with agents leading to iatrogenic hypoxic medullary injury, such as NSAIDs, calcineurin inhibitors or amphotericin, and stopping SGLT2i prior to radiocontrast studies.

9 Renin–Angiotensin–Aldosterone (RAAS) Blockers, SGLT2i, and the Kidney: Similarities and Differences

Inhibitors of the RAAS axis and SGLT2i share an immediate decline in GFR in common, which in the long run stabilizes with renal protection, as compared with controls. Indeed, the pattern of GFR changes over time in empagliflozin-treated patients [4] is almost identical to those on RAAS blockade, as shown with benazepril in the AIPRI (Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency) study, for example [73]. Furthermore, as illustrated in Table 3, both interventions improve renal cortical oxygenation, a factor that may be important in preventing hypoxia-mediated progressive renal disease [41, 81]. However, they differ in the mechanism of GFR reduction, with predominant efferent arteriolar vasodilation by RAAS blockade versus activation of the TGF mechanism and the restoration of diabetes-induced afferent arteriolar vasodilation with SGLT2 inhibition [18].

Consequently, and most important to the current discussion, these interventions diversely affect renal medullary oxygenation. RAAS blockade improves renal parenchymal oxygenation to some extent through

Table 3 Postulated renal physiologic changes: comparing the effects of renin–angiotensin–aldosterone axis blockade by angiotensin converting enzyme inhibitors or angiotensin II receptor blockers with the impact of sodium–glucose co-transporter-2 inhibition

	Glomerular filtration rate	Regional blood flow	Tubular transport activity	pO_2	Tubuloglomerular feedback
RAAS blockade	↓	Cortex ↑↔	Cortex ↓↔	Cortex ↑↔	↓
		Medulla ↑↔	Medulla ↓↔	Medulla ↑↔	
SGLT2 inhibition	↓	Cortex ?↓	Cortex ↓	Cortex ↑	↑
		Medulla ?↓	Medulla ↑	Medulla ↓	

pO_2 partial pressure of oxygen, *RAAS* renin–angiotensin–aldosterone, *SGLT2* sodium–glucose co-transporter-2, ↓ indicates decrease, ↑ indicates increase, ↔ indicates unknown

improved microvascular blood flow, but likely principally by reducing GFR and diminishing tubular transport and oxygen expenditure in both proximal and distal tubular segments [82–85]. In contrast, SGLT2 inhibition reduces proximal tubular oxygen expenditure but augments distal tubular transport activity and oxygen consumption, with intensified renal medullary hypoxia [21]. Therefore, though both RAAS and SGLT2 inhibition may potentially cause AKI, its pathogenesis might be different. RAAS blockade conceivably produces a reversible 'pre-renal' AKI by altering glomerular hemodynamics, usually in the presence of CKD, effective blood volume depletion, renal artery stenosis, or the administration of NSAIDs [86, 87]. This is likely due to exaggerated afferent arteriolar vasoconstriction and reduced trans-glomerular hydraulic pressure. In contrast, SGLT2 inhibition, in addition to diuresis-related pre-renal failure, may potentially lead to hypoxic AKI with tubular injury, conceivably in the presence of additional insults that intensify medullary hypoxia, such as the use of NSAIDs or calcineurin inhibitors or with exposure to iodinated radiocontrast agents. Combining RAAS blockade and SGLT2i might produce an accentuated decline in the trans-glomerular pressure gradient, which could intensify the likelihood of developing a pre-renal form of AKI, while perhaps alleviating medullary hypoxia and the risk to hypoxic AKI (due to markedly reduced GFR).

10 Conclusions and Future Directions

Prospective randomized studies with empagliflozin indicate that the incidence of AKI in treated patients does not increase and may even be attenuated. However, sporadic reports and additional retrospective analyses suggest that under certain conditions there might be an increased risk for AKI in patients treated with SGLT2i. Physiologic considerations support the likelihood that this treatment may predispose to AKI in certain conditions, leading either to a pre-renal form of AKI or to hypoxic AKI. Thus, we are left with a certain degree of uncertainty, and this debate deserves further evaluation. The renal safety of SGLT2i should be evaluated in experimental models of hypoxic AKI, using combined endpoints of renal dysfunction, morphology, biomarkers of renal parenchymal damage, and indices of hypoxic stress. Such studies might help compare the different SGLT2i available regarding renal safety and their direct impact on the renal oxygenation profile and microcirculation. Prospective additional clinical studies may be needed in particular to assess renal safety in patients with pre-specified clinical risk factors for either the pre-renal or renal forms of AKI detailed earlier (see Sects. 6–8). Lastly, hydration status and urine sediment as well as urinary biomarkers should be evaluated in patients with substantially declining kidney function while on SGLT2i. Plausible interactions between co-morbidities and concomitant medications with host-dependent genetic vulnerability should also be explored, though so far common genetic variants in the *SLC5A2* gene, encoding SGLT2, have not been found to clinically affect the response to SGLT2i [88].

In the meantime, it is suggested that kidney function and hydration status should be closely monitored with the initiation of SGLT2i, especially in patients predisposed to AKI, with adjustments made as needed to diuretics and RAAS blockers. We also propose that the concomitant use of SGLT2i and NSAIDs be avoided and treatment with SGLT2i be withheld prior to radiocontrast studies.

Compliance with Ethical Standards

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