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REVIEW

Is there any robust evidence showing that SGLT2 inhibitor use predisposes to acute kidney injury?

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Abstract

A novel class of oral glucose lowering drugs, sodium-glucose co-transporter type 2 inhibitors (SGLT2is), has shown additional beneficial effects on body weight, serum uric acid levels, blood pressure, and cardiac and renal function. Conflicting data have been published regarding the potential risk of acute kidney injury (AKI) when using SGLT2is. Aim of this manuscript was to review the current literature on this issue. SGLT2is induce a mild acute decline in estimated glomerular filtration rate, attributed to the effect of proximal tubular natriuresis on tubuloglomerular feedback through increased macula densa sodium delivery, leading to afferent arteriole vasoconstriction and reduced intraglomerular pressure. This functional effect with a subsequent rise in serum creatinine fulfills the creatinine-based criteria for AKI, as defined in clinical practice and trial settings. Other proposed potential mechanisms as to how SGLT2is lead to AKI include osmotic diuresis leading to volume depletion, increased urinary uric acid levels, intratubular oxidative stress, local inflammation and tubular injury. Despite the warning published by the US Food and Drug Administration in 2016 about a potential risk of AKI and the report of some clinical cases of AKI after treatment with SGLT2is, large observational real-life retrospective studies, randomized controlled trials and propensity-matched analyses of data from clinical practice unambiguously demonstrate that SGLT2is are safe for the kidney and do not predispose to AKI. In conclusion, while we can probably stop worrying about AKI risk when using SGLT2is, the question whether these agents should be withheld in the presence of clinical situations at high risk for AKI remains unaddressed.

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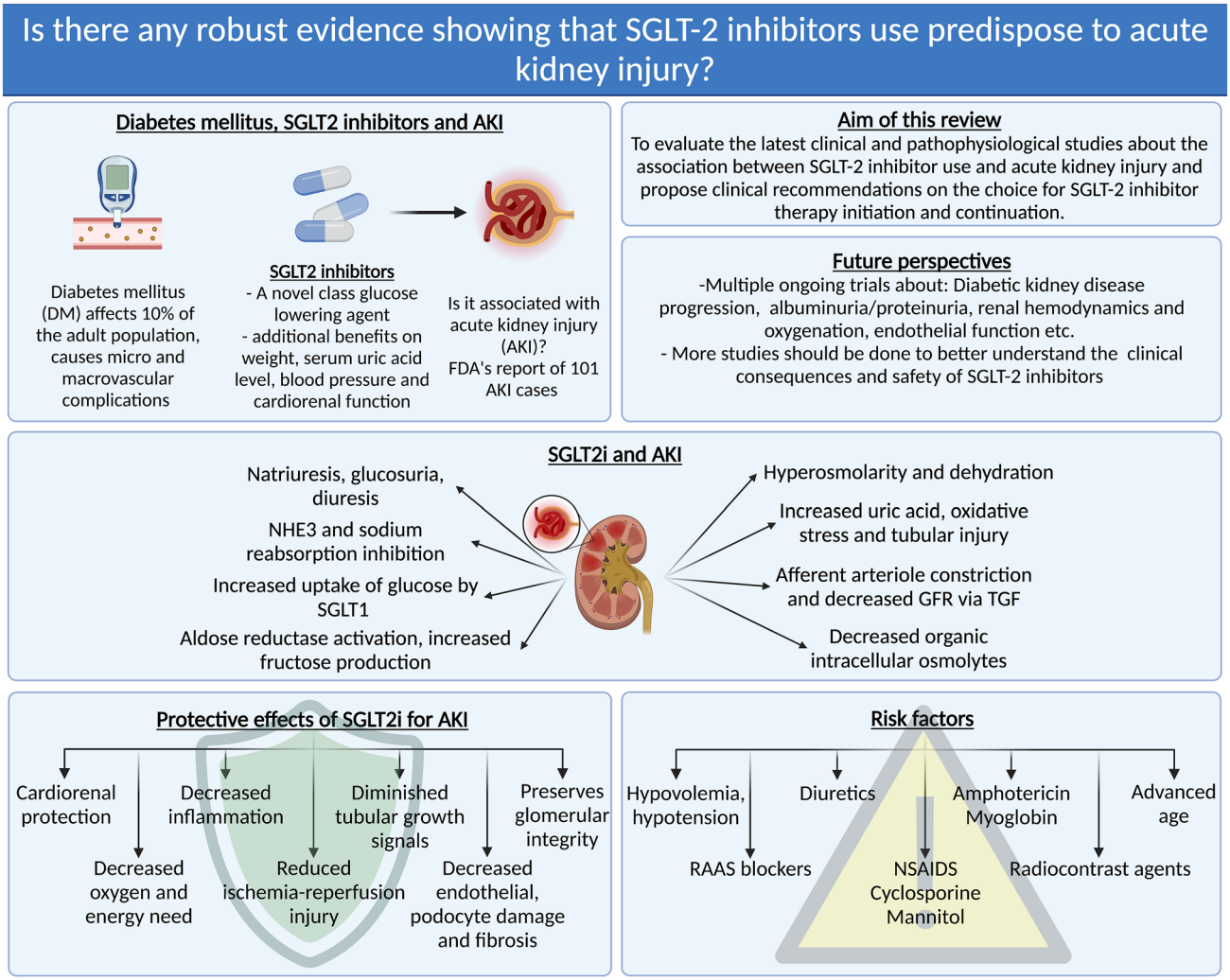
Graphical abstract



Keywords Acute kidney injury · Chronic kidney disease · Diabetes mellitus · Glomerular filtration rate · SGLT2 inhibitor

Introduction

Diabetes mellitus (DM) is among the most common chronic conditions globally, affecting approximately 10% of the adult population with significant long-term micro- and macrovascular complications. Diabetic nephropathy is the most common cause of chronic kidney disease (CKD), a condition listed among the top ten causes of annual mortality [1, 2]. Although angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) have been shown to be protective against the progression of diabetic kidney disease and albuminuria, this condition still causes significant morbidity and mortality, thus requiring proper management and therapeutic alternatives [3, 4]. A novel class of oral glucose lowering drugs, sodium-glucose co-transporter type 2 inhibitors (SGLT2is), has shown additional multiple beneficial effects [5–7]. Conflicting data have been published regarding the potential risk of acute kidney injury (AKI) when using SGLT2is [8, 9]. The US Food and Drug Administration (FDA) reported 101 cases of AKI in patients using SGLT2is [5]. Unfortunately, this report seems vague on AKI diagnostic tools and does not provide sufficient information, thus creating a debate. The aim of this review was to evaluate the association between AKI and SGLT2i therapy and its potential pathophysiological mechanisms.

Literature search strategy

Literature search was performed according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). It was performed in March 2022 on the PubMed/Medline, Web of Science, Scopus, Cochrane Library, and CINAHL databases by utilizing the listed terms or their combinations: "acute kidney injury", "acute kidney failure", "acute renal failure", "nephrotoxicity", "sodium-glucose co-transporter type 2 inhibitors", "SGLT-2", "SGLT-2 inhibitors", "canagliflozin", "dapagliflozin", "empagliflozin", "diabetes", "diabetes mellitus", "anti-diabetic drugs", "eGFR", and "estimated glomerular filtration rate". We screened the abstracts and titles of the studies that were identified through the search platforms mentioned above. References of the reviews and studies were additionally screened for relevant publications. The selected studies were further investigated in full text for relevance of the specified criteria. After the preliminary selection, full texts of the selected studies were independently evaluated by two of the authors (SC and AY) (Fig. 1).

Review of the literature

Table 1 shows the 22 studies in which the risk of AKI when using SGLT2is was analyzed: 10 were retrospective cohort studies [6–15]: among them, SGLT2i users were compared with non-SGLT2i users [12, 13, 15], with dipeptidyl-peptidase-4 inhibitor (DPP-4i) users [6–8, 10, 11, 14], oral glucose lowering drug users [9] and GLP-1 receptor agonist (GLP-1RA) users [8]. Follow-up periods for renal adverse effects or AKI incidence varied from 6 [8, 14] to 33 months [9] with a median of 19 months [11, 13]. Most of the cohort

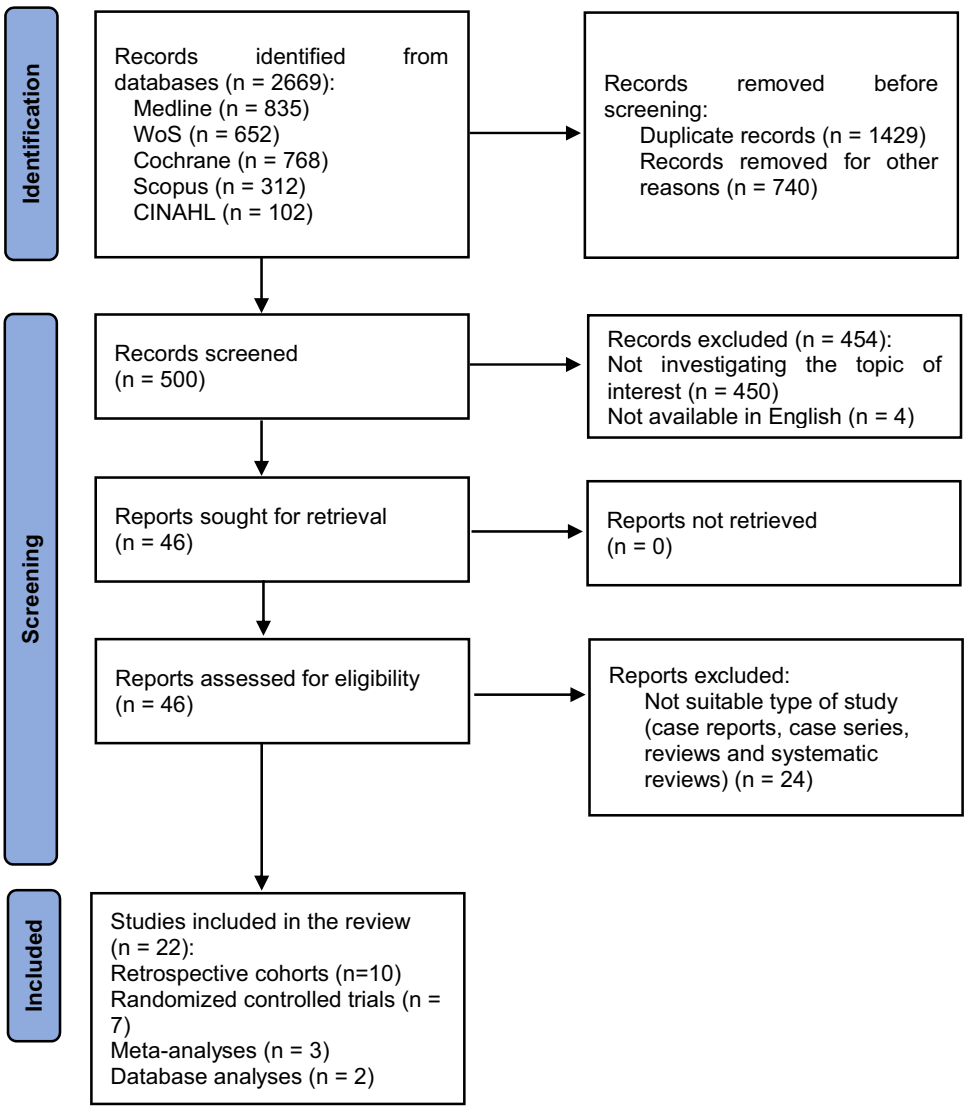


Fig. 1 Flow diagram of the study selection process

Table 1 Studies analyzing the acute kidney injury risk when using a sodium-glucose co-transporter type 2 inhibitor

References	Design	SGLT2i users (*N*)	Results	Follow-up
Nadkarni et al. [15]	1:1 propensity matched retrospective cohort study (SGLT2is vs. non-SGLT2is)	1584	No increased AKI risk	15 months
Neal et al. [21]	Randomized single-blind placebo-controlled trial (SGLT2is vs. placebo)	5795	No increased AKI risk	44.5 months
Cahn et al. [14]	Retrospective cohort study (SGLT2is vs. DPP-4is)	6418	No increased AKI risk	6 months
Donnan et al. [23]	Meta-analysis (SGLT2is vs. placebo)	6864	No increased AKI risk	–
Gilbert and Thorpe [25]	Meta-analysis of cardiovascular outcome trial	17,599	Decreased AKI risk	52 months
Menne et al. [24]	Meta-analysis	68,159	Decreased AKI risk (36%)	–
Lin et al. [13]	Retrospective cohort study (SGLT2is vs. non-SGLT2is)	7624	Lower incidence of eGFR decrease and no increase in AKI risk	18 months
McMurray et al. [22]	Phase 3 placebo-controlled trial (SGLT2is vs. placebo)	2373	Significantly fewer serious renal adverse events compared to placebo	24 months
Miyoshi et al. [12]	Retrospective longitudinal cohort study (SGLT2is vs. non-SGLT2is)	1337	Lower incidence of eGFR decrease	24 months
Perkovic et al. [20]	Double-blind, randomized placebo-controlled trial (SGLT2is vs. placebo)	2202	No increased AKI risk	31.5 months
Heerspink et al. [17]	Randomized double-blind placebo-controlled multicenter clinical trial (SGLT2is vs. placebo)	2152	Decreased risk of ESRD HR 0.64 (0.5–0.82)	29 months
Cahn et al. [16]	Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI randomized double-blind placebo-controlled trial (SGLT2is vs. placebo)	8582	Decreased AKI risk	50 months
Katsuhara et al. [26]	Analysis of Japanese Adverse Drug Event Report database (JADER) (SGLT2is vs. non-SGLT2is)	4322	No increased AKI risk; increased risk of ketoacidosis and urogenital tract infections	–
Cannon et al. [18]	Multicenter double-blind randomized placebo-controlled event-driven non-inferiority trial (SGLT2is vs. placebo)	5499	No increased AKI risk	42 months
Bakris et al. [19]	Randomized double-blind placebo-controlled multicenter international trial (SGLT2is vs. placebo)	84	No increased AKI risk and even slowed progression of kidney failure	30.5 months
Pasternak et al. [11]	1:1 propensity matched retrospective cohort study (SGLT2is vs. DPP-4is)	29,887	Reduced risk of serious renal events	20 months
Iskander et al. [10]	Retrospective cohort study (SGLT2is vs. DPP-4is)	19,611	Decreased AKI risk	26 months
Rampersad et al. [9]	1:1 propensity matched retrospective cohort study (SGLT2is vs. oral glucose lowering drugs)	4778	No increased AKI risk	33 months
Alkabbani et al. [6]	Population-based retrospective cohort study (SGLT2is vs. DPP-4is)	9608 (7712 + 1896)	No increased AKI risk	15 months
Katsuhara et al. [27]	Analysis of United States Food and Drug Administration's Adverse Event Reporting System records (SGLT2is vs. non-SGLT2is)	29,204	Increased AKI risk in monotherapy; AKI incidence reduced with the concommitant use of ACEis or ARBs	–
Lee et al. [7]	Propensity score-matched retrospective cohort (SGLT2-is vs. DPP-4is)	3521	Decreased AKI risk ($P < 0.001$) and slowed eGFR decline compared to DPP-4is	24 months
Zhuo et al. [8]	1:1 matched population based retrospective cohort study (SGLT2is vs. DPP-4is or GLP-1RA)	68,130	Decreased AKI risk compared to the DPP-4i group (HR 0.71, 0.65–0.76) or GLP-1RA (HR 0.81, 0.75–0.87)	6 months

SGLT2is, sodium-glucose co-transporter type 2 inhibitors, *AKI*, acute kidney injury, *DPP-4is* dipeptidyl-peptidase-4 inhibitors, *GLP-1RA* GLP-1 receptor agonists, *HR* hazard ratio, *RAASis* renin angiotensin aldosterone inhibitors, *ACEis* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *eGFR* estimated glomerular filtration rate

studies indicated no relationship between SGLT2i use and AKI incidence [6, 9, 13–15]. Lin et al. [13] also showed a statistically significant lower incidence of estimated glomerular filtration rate (eGFR) decline as reported in two other cohorts [7, 12]. Results from several studies showed a decline in adverse renal events [11] and risk for AKI with respect to their comparators [7, 8, 10]; interestingly Zhuo et al. [8] showed a decreased risk of AKI in SGLT2i users when compared to both DPP-4i and GLP-1RA users.

Seven randomized controlled trials (RCTs) are also included in Table 1: 5 were double-blinded randomized placebo-controlled trials [16–20], 1 was a single-blinded randomized placebo-controlled trial [21], 1 was a phase 3 placebo-controlled trial [22]. Follow-up period ranged from 24 [22] to 50 months [16], with a median of 31.5 months [20]. Four studies showed no link between SGLT2i use and AKI incidence compared to placebo [18–21], whereas, interestingly, Cahn et al. showed a decrease in AKI with the use of SGLT2is compared to placebo [16]. Additionally, studies reported fewer serious renal adverse events [22], decreased risk of end-stage kidney disease (ESKD) [17] and statistically significant slower progression of kidney failure [19].

Three meta-analyses [23–25] and 2 database analyses [26, 27] are also included in Table 1: SGLT2is were compared with placebo [23], non-SGLT2is [26, 27] or not defined [24, 25]. Results showed no association of AKI with SGLT2i use [23, 26], decrease in AKI incidence [24, 25], increasing AKI incidence [27]. These different data make it harder to interpret results and to provide precise management plans. Interestingly, Katsuhara et al. pointed out that AKI incidence was reduced with the concomitant use of ACEis or ARBs [27].

AKI risk factors in SGLT2i use are summarized in Table 2: while no additional AKI risk due to the concomitant use of ARBs or ACEis with SGLT2is was reported by Rampersad et al. [9], Pasternak et al. [11] and Katsuhara et al. [27] reported a reduction in the risk of AKI by the concomitant use of ARBs or ACEis with SGLT2is. AKI risk with SGLT2i monotherapy was found to be 0.97, whereas it was 1.19 with the concomitant use of ACEis or ARBs [10]. Similarly, Lee et al. reported a statistically significant increase in the risk of AKI with the concomitant use of ACEis (1.5 vs. 2.2) [7].The concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and SGLT2is was reported to not increase AKI risk by Pasternak et al. [11]. Contrarily, concerns regarding the concomitant use of NSAIDs and SGLT2is were reported by Heyman et al.: their study suggested that the possible explanation for this effect could be that SGLT2is could lead to dehydration caused by osmotic diuresis and natriuresis, especially in patients treated with diuretics. It was also proposed that SGLT2is could cause an intensification of renal parenchymal hypoxia and hypoxic kidney injury. Therefore, these authors proposed avoiding the concomitant administration of NSAIDs that could lead to iatrogenic hypoxic medullary injury [28]. Furthermore, no AKI risk due to the concomitant use of SGLT2is and diuretics was found in the study by Pasternak et al. [11] or in the study by Rampersad et al. [9]. On the contrary, Iskander et al. found that the AKI risk was 0.85 without any diuretic use and 2.01 with the concomitant use of a diuretic [10]. Similarly, the AKI risk was 1.4 without any diuretic use and 6.6 with the concomitant diuretic use in the study by Lee et al. [7]. Miyoshi et al. reported that the initial decrease in eGFR was statistically significantly smaller in patients who discontinued diuretics compared with those who continued them ($P = 0.004$) [12].

AKI risk was shown to be higher with increasing age: incidence rates of 4.2, 5.4, and 9.3 cases per 1000 person-years were reported in age groups < 65, 65 to 75, and > 75 years, respectively ($P < 0.0001$) [16]. Perkovic et al. reported that SGLT2is were protective at the baseline urinary albumin-to-creatinine ratio (UACR) > 1000 mg/g; SGLT2is had no beneficial effects when the baseline UACR was ≤ 1000 mg/g [20]. AKI risk in patients aged < 80 years was 1.04% and 1.84% in patients aged ≥ 80 years in the study by Iskander et al. [10]. McMurray et al. similarly reported a slight increase in the AKI risk when comparing < 65 years with ≥ 65 years of age: 15.7 vs. 16.7 [29]. The studies by Heerspink et al. [17] and Pasternak et al. [11] found that SGLT2i were protective in all age groups. Lastly, Lee et al. showed a gender difference, i.e., AKI risk rate lower in female than in male patients (2.18 vs. 3.56%) [7].

Temporarily withholding SGLT2is along with diuretics, metformin, NSAIDs, and renin–angiotensin–aldosterone system (RAAS) blocking agents under conditions of intercurrent illness, or procedures involving contrast materials is a reasonable approach given the minimal clinical downside to discontinuing these agents for a few days until the patient is back to his/her baseline state [30]. Figure 2 summarizes the AKI risk factors when using SGLT2is, the pathophysiological mechanisms through which AKI could occur and the measures that should be taken to prevent AKI occurrence. Prevention methods shown in Fig. 2 are based on the recommendations of the best clinical practice; it must be acknowledged that clinical studies demonstrating the effectiveness of such actions are lacking.

Do SGLT2is predispose to AKI?

In healthy individuals the glucose filtered from the glomeruli is reabsorbed by SGLT2 located at the S1 segment of the proximal tubules (80–90%) and by SGLT1 located at the S2–S3 segment of the proximal tubules (the remaining 10–20% of the filtered glucose) [30] (Fig. 3). In contrast to the wider distribution of SGLT1 in the human body, SGLT2 is found in the cerebellum and α-cells of pancreatic Langerhans islets as well as in the proximal kidney tubules [31].

Table 2 Acute kidney injury risk factors when using sodium-glucose co-transporter type 2 inhibitor

References	RAASis (ARBs and ACEis)	NSAIDs	Diuretics	Age group or patient group risk factors	Other mentioned risk factors
McMurray et al. [22]	N/A	N/A	N/A	Slight increase with age: < 65 years vs. ≥ 65 years: 15.7 vs. 16.7	N/A
Miyoshi et al. [12]	N/A	N/A	Significantly smaller initial decrease in eGFR in patients who discontinued diuretics compared with those who continued diuretics ($P = 0.004$)	N/A	N/A
Perkovic et al. [20]	N/A	N/A	N/A	UACR at baseline > 1000 1000 mg/g: SGLT2i protective; UACR at baseline ≤ 10,001,000 mg/g: SGLT2i no beneficial effect	N/A
Rampersad et al. [9]	No effect modification by RAASis ($P = 0.9$)	N/A	No effect modification by diuretics ($P = 0.8$)	N/A	N/A
Cahn et al. [16]	N/A	N/A	N/A	Higher rates of AKI with increasing age: incidence rates of 4.2, 5.4, and 9.3 cases per 1000 person-years in age-groups < 65, 65–75, and > 75 years, respectively ($P < 0.0001$)	N/A
Pasternak et al. [11]	No increased AKI risk with the concomitant use of RAASis	No increased AKI risk with the concomitant use of NSAIDs	No increased AKI risk with the concomitant use of diuretics	Protective in all groups	N/A
Heerspink et al. [17]	N/A	N/A	N/A	Protective in all groups	N/A
Iskander et al. [10]	Monotherapy with SGLT2is = 0.97; concomitant use of baseline ACEis or ARBs = 1.19	N/A	No baseline diuretic use = 0.85; any diuretic class = 2.01	Age < 80 (1.04) Age ≥ 80 (1.84)	N/A
Katsuhara et al. [27]	Reduced AKI risk with the concomitant use of ARBs or ACEis	N/A	N/A	N/A	N/A
Lee et al. [7]	no-ACEi use: 1.5 ACEi use: 2.2	N/A	No diuretic use: 1.4 Diuretic use: 6.6	N/A	A lower rate of AKI in females than in males (2.18 vs. 3.56%)

UACR urinary albumin-to-creatinine ratio, *N/A* not applicable, *RAASis* renin angiotensin aldosterone inhibitors, *ACEis* angiotensin converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *AKI* acute kidney injury, *SGLT2is* sodium-glucose co-transporter type 2 inhibitors

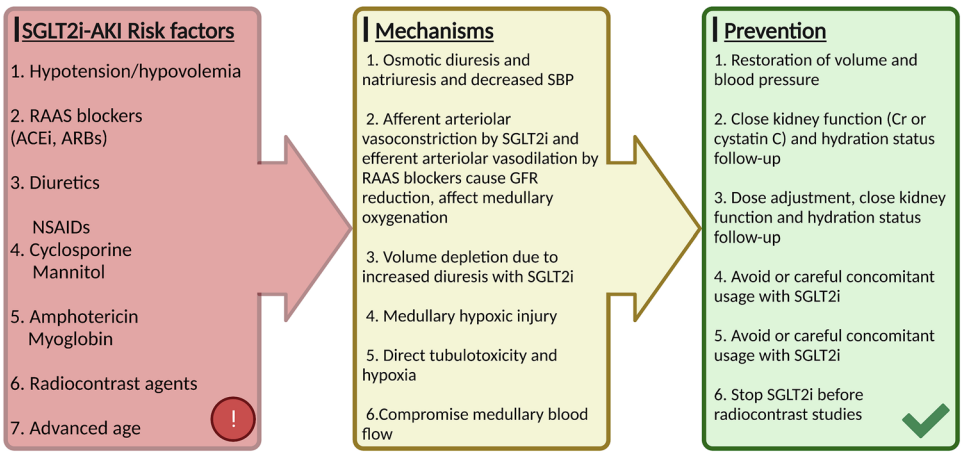


Fig. 2 Risk factors for acute kidney injury (AKI) related to SGLT2is and associated conditions/medications. *RAAS* renin–angiotensin–aldosterone system, *ACEis* angiotensin converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers, *NSAIDs* non-steroidal anti-inflammatory drugs, *SBP* systolic blood pressure. (Same numbered points in different columns indicate the same entity)

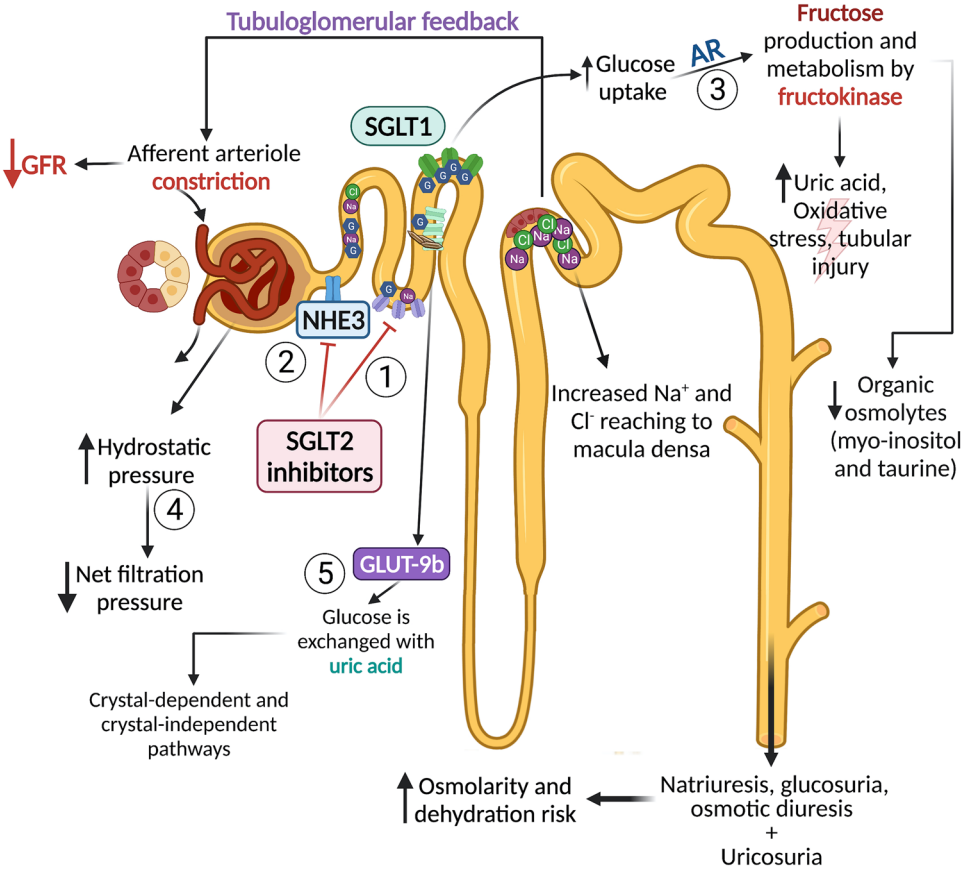


Fig. 3 Blockage of diabetes mellitus-induced hyperfiltration by SGLT2is. The decreased sodium (Na) and glucose (G) absorption through SGLT2is increases the amount of Na and chloride (Cl) delivered to macula densa. Via tubuloglomerular feedback, afferent arterioles are constricted and glomerular filtration rate (GFR) is decreased. SGLT2is also block sodium-hydrogen transporter (NHE3) and Na reabsorption

SGLT2is have been shown to reduce the progression of kidney failure by lowering glycated hemoglobin, blood pressure, body weight, and albuminuria [21, 32, 33]. The large urinary loss of glucose and sodium caused by SGLT2 transporter blockage raises the risk of hyperosmolarity and dehydration. Urine glucose may also be reabsorbed in exchange for uric acid by the glucose transporter GLUT9b, which is found in the apical membrane of proximal tubular cells. This exchange causes a 5–10% drop in serum uric acid levels, as well as increased uricosuria. A decrease in serum uric acid levels results in a decrease in systemic and glomerular hypertension in experimental animals, suggesting a relationship between uricosuria and the blood pressure lowering actions of SGLT2is [34]. On the other hand, an increase in urinary uric acid levels may be a risk factor for AKI via crystal-dependent and crystal-independent pathways. While uricosuria is a well-known cause of acute tumor lysis syndrome, evidence suggests that it may also play a role in other

types of AKI, such as that caused by radiocontrast agents, rhabdomyolysis, heat stress, and, most importantly, dehydration, which is recognized as a possible cause of AKI when using SGLT2is [35]. As a result, transport of high amounts of glucose through the tubule may activate the osmolarity-sensitive gene encoding aldose reductase. Aldose reductase induction results in the production of sorbitol and fructose. Fructose is metabolized by fructokinase, which is abundant in the S3 segment, resulting in the production of uric acid, oxidative stress, release of chemokines, local tubular injury and inflammation. Furthermore, experimental models showed that this route can produce endogenous fructose in the renal cortex in type 1 DM, heat stress, or dehydration, and that it may partially cause renal damage in these conditions [34, 36] (Fig. 1).

Additionally, other intracellular organic osmolytes, such as myo-inositol and taurine are depleted at the same time in which sorbitol and fructose accumulate within the tubular cells. As a result, it could be speculated that SGLT2is may lead to tubular damage. Szelat et al. emphasized that using SGLT2i and RAAS blockers together results in a greater drop in trans-glomerular pressure, and that taking drugs like NSAIDs or radiocontrast agents together with SGLT2is can cause renal medullary hypoxic damage, which may lead to AKI [37].

SGLT2 reabsorbs glucose and sodium, which results in a reduced concentration of sodium and chloride in the tubular fluid reaching the macula densa, specialized epithelial cells located at the end of the thick ascending limb of Henle (Fig. 3). This leads to an increase in eGFR via tubuloglomerular feedback mechanisms involving the dilatation of afferent arterioles [38, 39]. On the contrary, SGLT2is induce a mild acute decline in eGFR, attributed to the effect of proximal tubular natriuresis on tubuloglomerular feedback through increased macula densa sodium delivery, leading to afferent arteriole vasoconstriction and reduced intraglomerular pressure [38, 39] (Fig. 3). Additionally, SGLT2is have also been linked to the inhibition of sodium reabsorption at the level of the proximal tubules via sodium-hydrogen transporter referred to as NHE3 (Fig. 3) [40]. Moreover, the higher amounts of electrolytes and glucose reaching the distal tubules lead to an increase in fluid volume of the distal tubule and thus to an increase in hydrostatic pressure of Bowman's capsule that is a negative regulator of net filtration pressure at the glomerular level [41] (Fig. 3).

Lastly, the shift of energy expenditure across the nephron from the S1 segment to the S3 segment of the proximal tubule, where SGLT1 is located, and to the medullary thick ascending limb leads to a decline in partial oxygen pressure in those regions and an enhancement of hypoxia-inducible factor signaling [42, 43]. Enhanced hypoxia-inducible factor signaling results in the upregulation of erythropoietin (EPO) and hemoxygenase-1 [44, 45].

Do SGLT2is protect from AKI?

Cassis et al. provided experimental evidence of the reno-protective effects of the SGLT2i dapagliflozin, which reduced podocyte damage, glomerular lesions and proteinuria in mice with non-diabetic kidney disease [46]. In accordance with this study, SGLT2 levels were found to be increased by albumin load both in in vivo and in vitro models in an NF-kB–dependent manner; SGLT2is limited cytoskeletal remodeling mediated by albumin load in a cultured podocyte environment leading to preservation of the tubuloglomerular integrity [46, 47]. SGLT2is also interfere in a reno-protective way with non-glycemic pathways [32, 48]. Furthermore, in experimental DM models SGLT2is reduced albuminuria, mesangial expansion, matrix accumulation and interstitial fibrosis via the combined effects on glomerular hemodynamics and inhibition of renal inflammation and oxidative stress [49–52].

Another in vitro basic science study showed that the SGLT2i empagliflozin was able to reduce the levels of inflammatory and fibrotic markers [53]. Reduced metabolic requirements of blocked co-transporters also reduces the risk of ischemic-reperfusion damage or renal tubular hypoxia [54]. A reduction in AKI risk might theoretically lead to improvements in CKD progression, offering a mechanistic explanation for the favorable effect of SGLT2i on eGFR slopes in people with heart failure but no albuminuria [55–58].

Peritubular cells can produce more EPO in response to lower oxygen tension in the medulla, which could explain why hematocrit levels are higher in these individuals [59]. Because of its immunomodulatory activities, restoring EPO levels may eventually contribute to renal tissue protection [60].

Hyperglycemia causes an increase in glucose filtration, which leads to an increase in glucose reabsorption in the proximal tubule. This, in turn, increases oxygen consumption and depletes oxygen delivery to the tubular distal areas, particularly the renal medulla [38, 61]. SGLT2is may enhance oxygen availability, minimize reactive oxygen species, and improve medulla viability by lowering glucose reabsorption. This is difficult to reconcile with findings that SGLT2is boost EPO synthesis, which is often associated with renal hypoxia [62]. However, it does help to account for a rise in hematocrit, which would help oxygen supply. To explain this dilemma, it has been proposed that SGLT2is alter the production or signaling of the hypoxia-inducible factor, reduce hypoxia-inducible factor-1 activity and/or promote hypoxia-inducible factor-2 activity in the kidney, favoring a decrease in pro-inflammatory and fibrotic factors while also increasing EPO levels [63, 64].

Lastly, various alternative pathways for SGLT2i renal protection have been suggested. The capacity to reduce blood pressure without increasing heart rate results in a decrease in sympathetic activity [65]. SGLT2is also reduce venous congestion and backpressure against renal venous drainage by reducing heart failure [66].

Dekkers et al. showed that dapagliflozin reduced albuminuria by 43.9% and eGFR by 5.1% compared to placebo. Dapagliflozin had no effect on glomerular charge or size selectivity index and reduced urinary excretion of IgG, IgG4, IL-6 and KIM-1; no changes in NGAL, LFABP, or MCP-1 were observed. Changes in albuminuria were shown to be linked to changes in eGFR and KIM-1. Finally, the albuminuria-lowering impact of dapagliflozin therapy for 6 weeks could be due to a reduction in intraglomerular pressure or tubular cell damage [67, 68].

It may be speculated that AKI can occur in the early phases, but due to inadequate measurements within 1–2 weeks of SGLT2i use, it might not be detected by clinicians. If not progressive, a slight initial reduction in GFR due to hemodynamic effects should be expected and tolerated [69]. Herrington et al. showed a small reversible reduction in eGFR in the first 4 weeks compared to placebo, followed by a significant reduction in the rate of chronic eGFR fall over time [70].

Five large scale RCTs have investigated the effects of SGLT2is on renal outcomes: the EMPA-REG outcome trial, the CANVAS program, CREDENCE, DAPA-CKD and EMPA-Kidney [17, 20, 21, 33, 70]. The EMPA-REG outcome trial investigated primarily the cardiovascular effects and secondarily renal outcomes of empagliflozin therapy for 192 weeks in 6185 participants with type-2 DM and high cardiovascular disease risk and eGFR > 30 mL/min/1.73 m^2. This trial reported an initial decline in eGFR in the empagliflozin group compared to the placebo group at 4-week follow-up (weekly decline of 0.62 ± 0.04 and 0.82 ± 0.04 mL/min/1.73 m^2 with 10 mg/day and 25 mg/day of empagliflozin, respectively); an increase of 0.01 ± 0.04 mL/min/1.73 m^2 was observed in the placebo group. The risk for incident or worsening nephropathy (12.7% vs. 18.8%), progression of macroalbuminuria (11.2% vs. 16.2%), doubling of serum creatinine (1.5% vs. 2.6%), and need for renal replacement therapy (0.3% vs. 0.6%) were lower in a statistically significant way in the empagliflozin group. No statistically significant change was observed in incident albuminuria (51.5% vs. 51.2%) [33, 71]. The CANVAS program included two RCTs with a total of 10,142 participants with a mean follow-up period of 188.2 weeks and investigated primarily the cardiovascular outcomes of canagliflozin therapy. The latter reduced the risk for albuminuria progression (89.4 vs. 128.7 participants with an event/1000 patient-years), the need for renal replacement therapy, death due to renal causes and eGFR decline in a statistically significant way compared to placebo [21]. Few other small scale studies investigated the renal outcomes associated with SGLT2is and reported contradictory findings. The limitation of such studies are the low number of participants and the short follow-up periods [72–78].

Therefore, the latest research has shown beneficial renal protective effects of SGLT2is, while the initial concerns raised by the US FDA Adverse Event Reporting System (FAERS) in 2016 with the announcement of 101 cases of SGLT2i-associated AKI in the first month following the initiation of therapy are mostly overcome by the growing literature [79]. Initial decline in eGFR and elevation in serum creatinine in diabetic patients are not caused by tubular or glomerular injury, and thus, do not impose additional risks for AKI. Figure 4 summarizes the mentioned pathophysiological mechanisms through which SGLT2is protect kidney function, as shown by the latest clinical and pre-clinical studies.

Conclusions

We can probably stop worrying about AKI risk when using SGLT2is. Despite the warning published by the US FDA in 2016 about a potential AKI risk and the report of some clinical cases of AKI when prescribing SGLT2is, large observational real-life retrospective studies, RCTs and propensity-matched analyses of data from clinical practice unambiguously demonstrate that SGLT2is are safe for the kidney and do not predispose to AKI. However, the question whether these agents should be withheld in the presence of high-risk clinical situations remains unaddressed.

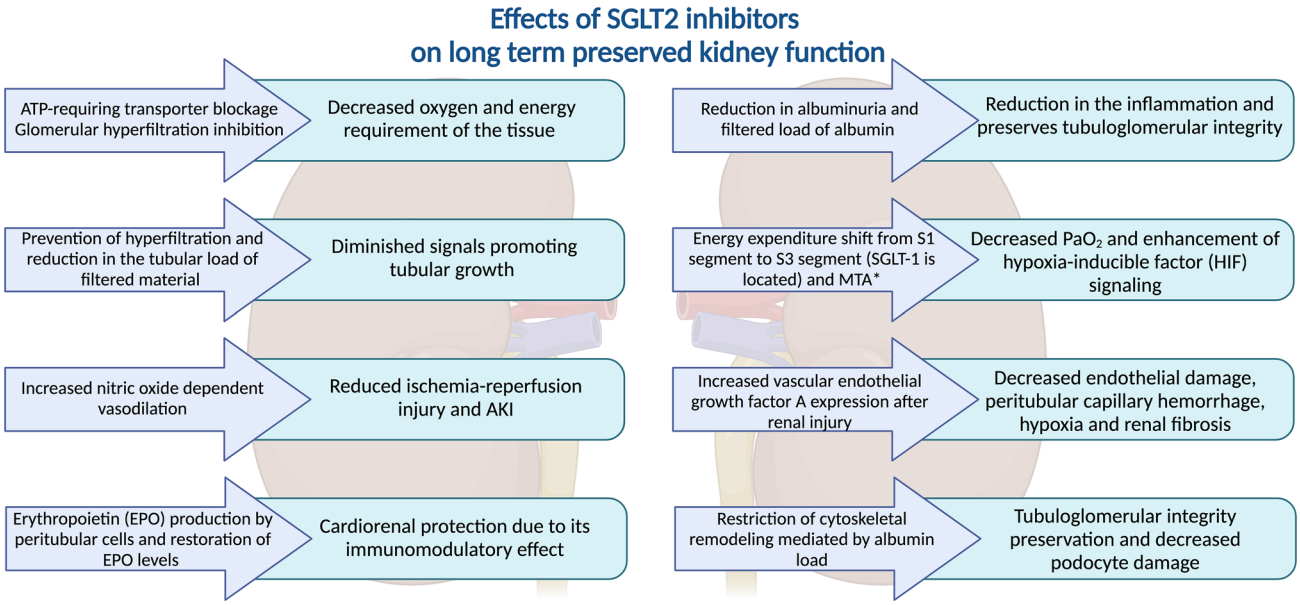


Fig. 4 Effects of SGLT2is on long-term preservation of kidney function. *MTA* medullary thick ascending limb, PaO_2 partial oxygen pressure in arterial blood

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Declarations

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Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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