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REVIEW

Considerations and possibilities for sodium-glucose cotransporter 2 inhibitors in pediatric CKD

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Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) were originally developed as glucose-lowering agents. These medications function by inhibiting glucose and sodium reabsorption in the S1 segment of the proximal tubule. Early clinical trials in adults with type 2 diabetes mellitus (T2DM) suggested a significant improvement in kidney and cardiovascular outcomes with SGLT2i therapy. Since then, SGLT2is have become a mainstay treatment for adult patients with CKD. A growing body of research has explored deploying these medications in new clinical contexts and investigated the mechanisms underlying their physiologic effects. However, patients under the age of 18 years have been largely excluded from all major trials of SGLT2i. This review aims to summarize the available clinical evidence, physiology, and mechanisms relating to SGLT2is to inform discussions about their implementation in pediatrics.

Keywords SGLT2 inhibitor · Pediatric CKD · Mechanisms

Introduction

Talking with any adult nephrologist, or opening any nephrology journal, quickly reveals the excitement surrounding sodium-glucose cotransport 2 inhibitors (SGLT2is). Such fanfare in the otherwise stoic field of nephrology has not been rivaled since the arrival of angiotensin-converting enzyme inhibitors (ACE-is), and possibly the Beatles before that [1–3]. A growing body of research suggests the enthusiasm is well-placed. Perhaps in part because treatment with SGLT2is improves outcomes for patients existing at the intersection of CKD, diabetes, and heart failure—a clinical context which has proven challenging in which to make progress.

To date, none of the major SGLT2i trials have included participants under the age of 18. Given their presumed longevity, the reno- and cardioprotective effects of SGLT2is might well serve children and young adults. However, several considerations require careful navigation prior to widespread implementation of SGLT2i therapy in pediatrics. The purpose of this review is to summarize the available evidence on SGLT2is and discuss clinical applications, adverse effects, and mechanistic insights relevant to children with CKD.

Currently available SGLT2 inhibitors

SGLT2is with FDA approval to lower blood sugar in adults with type 2 diabetes include canagliflozin ("Invokana," Janssen), dapagliflozin ("Farxiga," AstraZeneca), and empagliflozin ("Jardiance," Boehringer Ingelheim Pharmaceuticals). Major clinical trials of SGLT2is have utilized one of these three medications almost without exception. The comparative efficacy and safety between these SGLT2is appear similar, but reassessment might be warranted with ongoing collection of clinical trial data [4, 5].

SGLT physiology

Glucose is freely filterable at the glomerulus and nearly all is reabsorbed within the kidney tubule [6]. The incredible

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power of tubular reabsorption is illustrated by the fact that of ~ 180 g/day of glucose filtered, only around ~ 0.5 g/day is found in the urine [7]. There is a limit to the extent which glucose can be reabsorbed; under normal physiologic conditions, the maximum transport (T_m) of glucose occurs at a plasma concentration of 180 mg/dl. In diabetic individuals, this value can increase up to 400 mg/dl [6]. Around 90% of apical glucose reabsorption occurs through SGLT2 in the S1 segment of the proximal tubule. The remaining 10% is reabsorbed through SGLT1 in the S3 segment of the proximal tubule.

Research into SGLTs originated from studies of intestinal glucose absorption in the 1960s and 1970s [8]. Tissue expression of SGLTs is widespread (although SGLT2 is expressed almost exclusively in the proximal tubule), and their function is diverse [9]. SGLTs utilize the potential energy generated by sodium ions moving down their concentration gradient to transport glucose, amino acids, vitamins, osmolytes, and other organic anions [10]. This capability allows SLGT2 to transport glucose intracellularly from the tubule lumen against its concentration gradient [9]. In proximal tubular cells, intracellular glucose exits the basolateral membrane following its concentration gradient via the GLUT family of glucose transporters [7].

Development and mechanisms of SGLT inhibitors

Soon after their discovery and classification, SGLT1 and SGLT2 were both identified as therapeutic targets for patients with diabetes [8]. SGLT1 was targeted because it is the primary mediator of intestinal glucose absorption in addition to the small role it plays in tubular reabsorption of glucose. However, trials of SGLT1 inhibitors were unsuccessful, primarily due to untoward gastrointestinal side effects accompanying the increased load of unabsorbed intestinal glucose. Similar adverse events related to intestinal SGLT1 inhibition were also noted in studies of non-specific SGLT1/SGLT2 inhibitors.

Therefore, focus turned towards the therapeutic potential of SGLT2 blockade. The clinical effects of SGLT2 inhibition was already apparent in individuals living with autosomal recessive familial glycosuria related to mutations in SGLT2 [11]. Patients with this rare disorder have glycosuria at baseline but are otherwise healthy. Subsequently, SGLT2is were developed and demonstrated inhibition of SGLT2 via a competitive and reversible mechanism [12]. Most SGLT2is do demonstrate cross-reactivity with SGLT1, but the relative effect is trivial and clinically insignificant [13]. While some work has been undertaken to describe the pharmacokinetic and pharmacodynamic profile of SGLT2is in pediatrics, more research is required [14].

Clinical applicability: CKD

SGLT2is were initially conceived as glucose-lowering agents, and proved moderately successful in this regard [15]. The EMPA-REG trial was undertaken to satisfy an FDA requirement to demonstrate cardiovascular safety of glucose-lowering medications [16]. Following this, subsequent randomized control trials (RCTs) of SGLT2is with relevance to patients with CKD included Canagliflozin Cardiovascular Assessment Study (CANVAS), Canagliflozin and Renal Events in Diabetes with Established Nephropathy (CREDENCE), and Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD).

EMPA-REG (empagliflozin)

EMPA-REG randomized 7020 participants (≥ 18 years of age) to receive 10 mg or 25 mg empagliflozin or placebo. Study eligibility required a diagnosis of type 2 diabetes mellitus (T2DM), established cardiovascular disease, and eGFR ≥ 30 mL/min/1.73 m^2. At baseline, 26% of patients had an eGFR < 60 mL/min/1.73 m^2 and ~ 40% had either micro- or macroalbuminuria. Notably, mean age for study participants was 63 years.

A prespecified secondary analysis to examine the effects of empagliflozin on kidney outcomes was performed by Wanner et al. [17]. It utilized a composite outcome of incident or worsening nephropathy including the following components: incident macroalbuminuria, doubling of serum creatinine and eGFR ≤ 45, dialysis requirement, or kidney-related death. A second composite outcome of incident or worsening nephropathy or cardiovascular-related death was also used. This second outcome is likely more apropos given that most adults with CKD die from cardiovascular causes, and kidney-related death is a nebulous concept that is difficult to define or identify.

After 4 years of follow-up, participants randomized to treatment with empagliflozin had a relative risk reduction of 39% for incident or worsening nephropathy and 46% reduction when adding cardiovascular death to the composite outcome. Additionally, the rate of eGFR decline over the study period (up to 192 weeks) was significantly decreased in those randomized to empagliflozin. Preservation of eGFR occurred in a dose-independent manner, and empagliflozin use was associated with a + 4.7 mL/min/1.73 m^2 relatively higher eGFR at study end compared to placebo. The eGFR slope was most improved by empagliflozin use in those with a baseline eGFR > 60 mL/min/1.73 m^2.

CANVAS and CREDENCE (canagliflozin)

The CANVAS and the CREDENCE trials were the major RCTs of canagliflozin [18, 19]. Participants in both studies included individuals with T2DM over the age of 30 years. The CANVAS included participants with an eGFR ≥ 30 mL/min/1.73 m^2 (mean: 76 mL/min/1.73 m^2) and the CREDENCE included those with an eGFR between 30 and 90 mL/min/1.73 m^2 (mean: 56 mL/min/1.73 m^2).

The published results of the CANVAS trial in fact represent the integration of two nearly identical sub-trials [20]. Like EMPA-REG, the CANVAS was initially designed to assess cardiovascular safety. After interim analysis revealed a significant cardiovascular benefit for those randomized to canagliflozin, a parallel study using identical inclusion criteria and study administration was created (CANVAS-Renal). The primary outcome of this sub-study was progression of albuminuria (composite of > 30% increase, or progression of albuminuria classification), with a secondary composite endpoint of > 40% decline in eGFR for two sustained measurements, dialysis requirement, or death from kidney causes. Using the combined population of 10,142 participants, individuals randomized to canagliflozin experienced a ~ 30% reduced risk for progression of albuminuria and 40% reduced risk for composite kidney endpoint compared to those randomized to placebo.

The CREDENCE trial was the first trial of SGLT2is designed with a primary kidney outcome. A composite outcome measure was used and consisted of doubling of serum creatinine, progression to chronic kidney disease, or death from kidney or cardiovascular causes. At study completion, participants randomized to canagliflozin had a 30% lower relative risk for the primary outcome measure. Evaluating the individual components of the composite endpoint, canagliflozin use resulted in a risk reduction of 40% for doubling of creatinine, 32% for progression to chronic kidney disease, and 22% for cardiovascular death compared to placebo. The rate of GFR decline was significantly reduced in participants receiving canagliflozin. Additionally, albuminuria at study conclusion was significantly lower in those randomized to canagliflozin compared to placebo.

DAPA-CKD (dapagliflozin)

While conducted in adults, with a mean age of ~ 62 years, the DAPA-CKD trial is of greatest relevance to pediatric patients with CKD (Table 1) [21]. Unlike previous trials, a diagnosis of T2DM was not required for inclusion. Nevertheless, 68% had a diagnosis of T2DM at baseline. The DAPA-CKD aimed to enroll those aged ≥ 18 years with mild-to-moderate CKD (eGFR 25–75, study mean: 43 mL/min/1.73 m^2) with a UACr of 0.2–5 g/day. Stable use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blockers (ACE-i/ARBs) for at least 4 weeks prior to study enrollment was a requirement (although a tiny percentage of those with an absolute contraindication to ACE-i/ARB use was allowed to enroll). Notable exclusion criteria included T1DM, polycystic kidney disease, lupus nephritis, ANCA-vasculitis, or patients who had received immunotherapy for kidney disease < 6 months prior to enrollment. The trial was stopped early at 36 months due to efficacy.

A total of 4304 participants were randomized to receive either dapagliflozin or placebo. The primary outcome was a composite kidney endpoint consisting of > 50% decrease in eGFR, progression to chronic kidney disease, or death from kidney or cardiovascular causes.

Compared to placebo, treatment with dapagliflozin was associated with a significantly reduced hazard ratio (HR) for the composite kidney endpoint (HR: 0.61, 95% CI: 0.51–0.72). Stratified analyses demonstrated a similar effect size for those with an eGFR above or below 45 mL/min/1.73 m^2 at baseline and for participants with or without a diagnosis of T2DM at baseline. Following the hitherto pattern, participants randomized to dapagliflozin had a significantly slower rate of eGFR decline compared to placebo (-2.86 ± 0.11 mL/min/1.73 m^2 per year vs. -3.79 ± 0.11 mL/min/1.73 m^2 per year).

DAPA-CKD: IgA nephropathy

A prespecified, subgroup analysis of the DAPA-CKD trial repeated the primary analysis using only 270 participants with a CKD etiology of IgA nephropathy [22]. Diagnosis of IgA nephropathy was biopsy-proven in 94% of participants. When compared to the larger DAPA-CKD cohort, the baseline characteristics of the IgA subgroup were somewhat distinct. Mean age was 51 years and only 14% of participants had T2DM. At baseline, all participants were taking an ACE-i/ARB.

For those with IgA nephropathy included in the DAPA-CKD trial, participants randomized to dapagliflozin had a 71% decrease in their relative risk for the primary composite kidney outcome compared to placebo. When removing cardiovascular death from the composite endpoint, there was a 76% decrease in risk. Over 3 years of follow-up, the yearly rate of eGFR decline was 1.2 mL/min/1.73 m^2 worse in patients randomized to placebo compared to dapagliflozin.

Clinical applicability: heart failure

For patients with CKD, heart failure is the most common manifestation of cardiovascular disease and portends significant morbidity and mortality [23]. While heart failure may seem like a distant concern to pediatric nephrologists caring for children, young adults (18–40 years) with CKD experience heart failure at relatively high rates [24]. Many of

Table 1 Summary of the Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) and DAPA-CKD IgA subgroup trials. Of the existing large, randomized control trials, these are most relevant to pediatric patients with CKD

Trial	DAPA-CKD		DAPA-CKD IgA	
Inclusion criteria	Age ≥18 years, eGFR 25–75, UACR 0.2–5 g/day, ACE-i/ARB use × 1 month		Same as DAPA-CKD plus baseline diagnosis of IgA nephropathy (94% biopsy confirmed)	
Exclusion criteria	Polycystic kidney disease, vasculitis, immunosuppressive therapy < 6 months prior, type 1 diabetes, history of transplant		Same as DAPA-CKD	
Participants	4304		270	
Mean age	62 years		51 years	
Mean baseline GFR	43 mL/min/1.73 m^2		44 mL/min/1.73 m^2	
Primary outcome	> 50% decline in GFR, ESKD, or death due to kidney or cardiovascular etiology		Same as DAPA-CKD	
	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Hazard ratio (95% CI) for 1° outcome	0.61 (0.51, 0.72)	*1.0 ref*	0.29 (0.12, 0.73)	*1.0 ref*
Rate of GFR decline	− 2.9 mL/min/1.73 m^2 per year	− 3.8 mL/min/1.73 m^2 per year	− 3.5 mL/min/1.73 m^2 per year	− 4.7 mL/min/1.73 m^2 per year

the intermediate cardiovascular outcomes noted in research of children with CKD, including increased left ventricular mass, vascular stiffness, and hypertension, are important risk factors for the development of heart failure [25, 26].

How may treatment with SGLT2is benefit pediatric patients with CKD in this regard? The existing literature demonstrates consistent improvement in cardiovascular outcomes with SGLT2i use. However, envisioning how this applies to young patients with CKD remains unclear. The study populations employed by existing trials differ vastly from the pediatric CKD population (i.e., high rates of prevalent cardiovascular disease, cumulative exposures to smoking and alcohol, advanced age). Additionally, heart failure outcomes were often defined by hospitalization rates for heart failure, which may have a wide range of clinical significance. A secondary analysis of the DAPA-CKD trial stratifying participants by baseline heart failure status provides an intriguing observation [27]. For participants without heart failure at baseline, dapagliflozin use was associated with a 60% relative risk reduction for heart failure hospitalization (compared to a 38% relative risk reduction in those with prevalent heart failure). One possible interpretation is that SGLT2 inhibitors might function as a preventative measure against the development of heart failure, a relevant and important consideration for young people with CKD [28].

The utility of SGLT2is in preventing and/or improving outcomes in heart failure with preserved ejection fraction (HFpEF) may also be of relevance for young people with CKD. HFpEF is characterized by significant diastolic dysfunction with an ejection fraction > 50%. It is estimated that HFpEF accounts for at least 50% of prevalent heart failure in adult patients with CKD [29]. Pertinent to young CKD patients, reduced GFR, anemia, hypertension, and increased left ventricular mass have all been shown to be significant risk factors for HFpEF [30, 31].

However, existing trials of SGLT2is did not differentiate between HFpEF and heart failure with reduced ejection fraction (HFrEF) when assessing heart failure at baseline or as an outcome. To address this knowledge gap, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR) and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trials were constructed to examine the effectiveness of SGLT2is for improving HFpEF outcomes. Initial results from the EMPEROR trial demonstrate a significant reduction in risk for admission for heart failure or cardiovascular death in those randomized to treatment (HR: 0.79, 95% CI: 0.69, 0.90) [32]. Further results from these industry-sponsored trials are forthcoming.

While evidence describing how SGLT2is might improve heart failure outcomes in pediatric CKD is missing, SGLT2i use may disrupt the mechanisms that connect CKD with heart failure. Results from small laboratory and clinical studies indicate that SGLT2 inhibition results in subtle

improvements in ventricular mass, diastolic function, and endothelial function [33, 34].

Adverse effects

Urinary tract infections

All clinical trials were carefully monitored for the development of urinary tract infections (UTIs). While EMPA-REG noted a slight increase in risk for UTI with empagliflozin use, subsequent research has questioned the extent that SGLT2i therapy increases risk for UTI [35]. Patient populations included in the major SGLT2i trials were at elevated risk for UTIs at baseline, especially those with T2DM. Post-marketing studies have been equivocal [36]. Similarly, Fourier's gangrene has been a reported adverse event with SGLT2i use, but causality has yet to be proven definitively [37–39].

The risk for UTI with SGLT2is may manifest in a more pronounced way in children with CKD. First, few pediatric CKD patients would have glucosuria at baseline. Secondly, high urine glucose concentrations in patients with CAKUT and abnormal urinary flow due to reflux, obstruction, or need for mechanical catherization could be problematic. Little evidence in the adult literature is available to guide best practices for SGLT2is in these populations.

Ketoacidosis

Ketoacidosis occurred at rate of 0.05–0.1% in major SGLT2i trials [40]. In patients with type 1 diabetes (T1DM) the rate was 3–6%, prompting the FDA not to extend approval for SGLT2is in patients with T1DM pending further research [41]. Other identified risk factors for ketoacidosis include dehydration, prolonged fasting, and T2DM with insulin dependence [42].

Euglycemic ketosis occurs in most patients treated with SGLT2is. The detailed mechanisms by which SGLT2is lead to ketosis and ketogenesis are beyond the scope of this discussion but have been detailed further in several interesting reviews [40, 42]. Briefly, animal models suggest SGLT2is stimulate ketogenesis secondary to net body glucose loss, alterations in relative concentrations of insulin and glucagon, and increased lipolysis and fatty acid oxidation. The kidney may also play a central role in the development of ketosis as serum ketones are normally eliminated via urine. Experimental evidence is conflicting, but SGLT2 inhibition may have effects on urine elimination of ketones [40].

Additionally, it is important not to conflate ketosis and ketoacidosis in this setting. Ketosis itself is a benign process associated with SGLT2is. In fact, inducing ketosis through a ketogenic is being investigated to improve cardiovascular and weight outcomes in adolescents with obesity [43]. It is only when ketogenesis becomes unregulated, especially in the physiologic context of insulin insufficiency, does ketoacidosis precipitate. Insulin deficiency may also lead to biochemical changes in the proximal tubule that further alter ketone reabsorption and base losses in the urine [42].

Research to develop strategies to minimize the risk for ketoacidosis with SGLT2 inhibition, especially for patients with T1DM, is ongoing.

Effects on mineral bone disease of CKD

The effects of SGLT2 inhibition on bone health has been both a point of concern and controversy. An analysis using data from the CANVAS study found the rate of fractures was significantly higher in participants randomized to canagliflozin (4% vs. 2.6%) [44]. However, the difference in fracture rates in the DAPA-CKD trial was not as pronounced (4% vs. 3.2%, $p=0.22$). Additional studies examining differences in bone density between those with and without SGLT2i use have produced conflicting results [45, 46].

Several studies have documented the effects of SGLT2is on calcium-phosphorus-PTH homeostasis. Increases in serum phosphorus, PTH, and FGF-23, accompanied by decreases in serum vitamin D and urine phosphorus, appear as soon as 24 h after initiation with canagliflozin [47]. Another cross-over study of 31 adult patients with diabetic nephropathy demonstrated these laboratory trends remained significantly different 6 weeks after starting therapy [48].

So arises a paradox: How can SGLT2is improve cardiac and kidney outcomes in patients with CKD while at the same time worsening presumed meditators of poor cardiac and kidney outcomes in patients with CKD? Possibly, the protective mechanisms generated by SGLT2 inhibition outweigh the negative effects of elevated phosphorus, PTH, and FGF-23. Alternatively, ongoing SGLT2i research may call into question the axiomatic belief of direct pathogenic roles played by phosphorus, PTH, and/or FGF-23 in patients with CKD. Regardless of the eventual outcome, exciting opportunities for new research await.

Protective mechanisms

Several mechanisms have been proposed to explain the beneficial effects of SGLT2is (Fig. 1). Considering the modest efficacy of SGLT2is to lower hemoglobin A1c, and the number of non-diabetic patients who benefit from therapy, improved outcomes do not solely reflect improved glycemic control.

Glomerular hemodynamics and albuminuria

Glomerular hyperfiltration is a pathologic feature of diabetes, hypertension, and CKD and contributes to disease

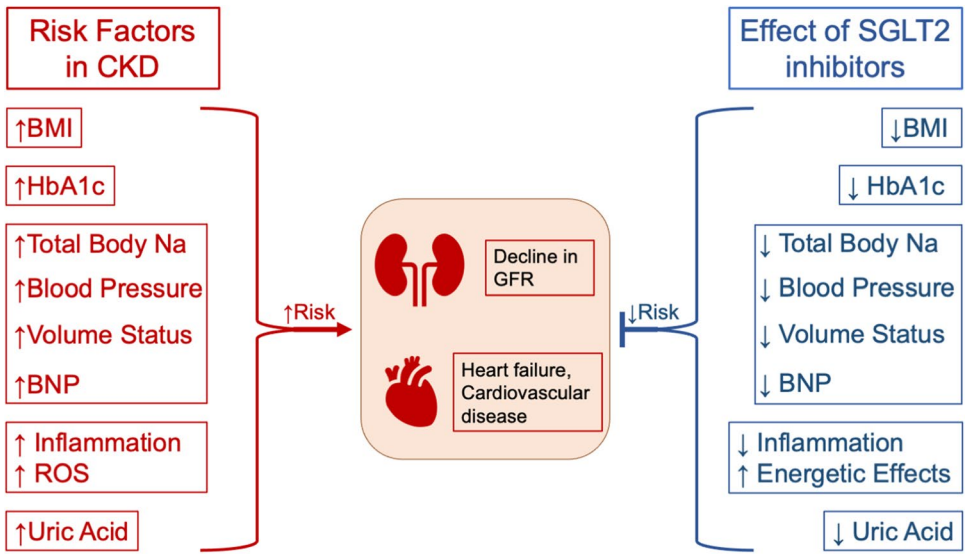

Fig. 1 Effects of sodium-glucose cotransporter 2 inhibitors on identified risk factors for CKD progression and cardiovascular disease in patients with CKD. BMI, body mass index; HbA1c, glycosylated hemoglobin; BNP, b-type natriuretic peptide; ROS, reactive oxygen species

progression. SGLT2is may improve hyperfiltration akin to ACE-i/ARBs. Major trials of SGLT2is have noted an acute drop in GFR with initiation of therapy [49]. Similar effects have been noted in pediatric studies. In a study of 27 adolescents with T2DM, single dose of empagliflozin was associated with a mean eGFR change of − 5.5 mL/min/1.73 m^2 after 24 h [50]. Another study of 40 young adults (mean age 24 years) with T1DM demonstrated reductions of inulin-measured GFR after 8 weeks of treatment with empagliflozin [51]. Change in eGFR was most pronounced in those with hyperfiltration (eGFR > 120 mL/min/1.73 m^2) at baseline. Neither of these studies included participants with eGFR < 60 mL/min/1.73 m^2. Acute decreases in GFR with SGLT2i therapy is postulated to occur through re-establishment of tubuloglomerular feedback mechanism [52].

Clinical trials also noted a significant reduction in proteinuria with SGLT2is. In the IgA subgroup analysis of the DAPA-CKD trial, participants randomized to dapagliflozin had a 30% reduction in UACr at 3 years compared to a ~ 0% change with placebo [22]. More research is required to understand how SGLT2is may best augment ace-inhibition to this extent.

Natriuresis, volume status, and blood pressure

Reducing tubular sodium reabsorption might not have been the primary focus when developing SGLT2is, but it may turn out to play a key role in their effectiveness. Elevated total body sodium and volume overload are both insidious and ubiquitous in patients with CKD. In adult patients, they are closely associated with hypertension, cardiovascular disease, and GFR decline [53]. Less is known in the context of pediatric CKD, but research is ongoing. Studies have shown that SGLT2is induce natriuresis, reduce plasma volume, and decrease blood pressure [54]. Additional studies have shown sustained decrease in plasma volume, skin sodium, and body weight [55, 56]. Possibly related to changes in body sodium, SGLT2i use results in a sustained decrease of 3–10 mmHg in systolic blood pressure [57].

Metabolic shifts

It may be no coincidence that the two organs that appear to benefit most from SGLT2 inhibition, the kidney and heart, are both voracious consumers of ATP. Studies suggest SGLT2is shift metabolism away from glucose oxidation and towards ketone and fatty acid oxidation [58]. It has been postulated that inhibition of SGLT2 on proximal tubule cells mimics a starvation state and generates protective effects through activation of the SIRT/AMPK pathway [59, 60]. While the specifics are still being explored, the net result confers several advantages. Decreases in tissue adiposity and intracellular lipid concentrations have been noted with SGLT2is [54]. Myocardial and proximal tubule tissues may utilize oxygen more efficiently, reducing the generation of free radicals. Taken together, these effects could ameliorate inflammation associated with diabetes and/or CKD [61]. Further research is investigating epigenetic effects relating to these metabolic shifts, potentially laying the foundation for sustained, long-term benefit [62].

Uric acid

A large body of pediatric research has connected elevated serum concentrations of uric acid with adverse

cardiovascular and kidney outcomes [63]. The direct pathogenic role of uric acid remains somewhat controversial. Convincing mechanisms relating uric acid to adverse outcomes have been identified. Randomized trials of uric acid lowering in adults have failed to demonstrate any benefit [64].

All controversies aside, SGLT2i therapy reduces serum uric acid concentration through increased urinary elimination [65]. Several mechanisms have been proposed: increased tubular glucose results in competitive inhibition of urate reabsorption in the proximal tubule [66]; also, proximal tubular uptake of urate may be linked to sodium reabsorption, which is reduced with SGLT2is [67].

Conclusions

In sum, SGLT2is have demonstrated great potential to transform the care for adults with CKD. There are many reasons to believe pediatric patients with CKD may benefit in a similar fashion. It is incumbent on all pediatric nephrologists to do whatever is necessary to ensure our patients with CKD live long, meaningful lives. The presumed longevity of pediatric patients with CKD has several implications. With every additional year of life comes an additional year living at risk for progression of their CKD and cardiovascular disease. Viewing this reality from a more optimistic angle, even modest reductions in risk at a young age have the potential to compound over a lifetime to great benefit for the patient. The ability of SGLT2is to slow GFR decline best embodies this potential [68]. One year after starting an SGLT2i, there may be a negligible difference in GFR. Assuming the effect is long-lasting, at 10 years, treatment with an SGLT2i might mean the difference between living with moderate CKD and its more severe forms.

Which pediatric patients with CKD warrant consideration for early trials of SGLT2is? It might be best to start with the patient groups to avoid. Given the risk for UTIs, patients with reflux nephropathy or obstructive CAKUT should be approached cautiously. Since the risks associated with SGLT2i therapy on bone health and growth are unknown, prepubescent patients might also require caution until more research is undertaken. Lastly, T1DM patients should avoid SGLT2i therapy until strategies to reduce the risk for ketoacidosis are identified. Ongoing pediatric trials of SGLT2i in patients with T1DM may be informative in this regard. Most notably, the ATTEMPT trial (Clinicaltrials.gov identifier: NCT04333823) is an RCT assessing the efficacy of dapagliflozin versus placebo to modulate glomerular hyperfiltration and metabolic parameters in adolescents with T1DM.

Adolescents with CKD, especially due to diabetic or IgA nephropathy, have a higher potential to benefit from SGTL2is, especially patients with signs of early cardiovascular disease. Biomarkers such as elevated uric acid, echocardiographic abnormalities, or signs of volume overload might help identify young patients most likely to benefit from SGLT2i therapy. Patients with vasculitic etiologies of CKD or kidney transplants were excluded from clinical trials in adults. While there is less data to inform SGLT2i use in these populations, they may warrant inclusion in future pediatric trials [69].

There also must be discussion of the socioeconomic impact. Young patients with CKD already experience a heavy pill burden, and non-adherence is a common challenge [70]. How will adding yet another medication improve outcomes?

Many of the beneficial effects of SGLT2is share characteristics with ACE-i/ARBs but come at a greater financial cost. Nonetheless, there may be additional and/or unique benefits of SGLT2is. One post hoc analysis of the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial found the risk reduction associated with dapagliflozin use was similar regardless with or without concurrent use of an ACE-i/ARB [71, 72]. Even so, optimizing ACE-i/ARBs may be a more economical first step pending further studies [73]. The question of whether ACE-i/ARB therapy was optimized and/or maximized in participants of the major SGLT2i trials is not easily ascertained in the existing literature.

In conclusion, pediatric patients deserve consideration for inclusion in ongoing research of SGLT2is. Collaboration with adult nephrology colleagues, along with consideration of the physiology and existing research on SGLT2is, can inform these efforts. Future pediatric CKD trials can also be informed by the results of ongoing SGLT2i trials in young people with T1DM and other conditions. A judicious approach is required, but there are many reasons to hope our young patients can benefit from this breakthrough therapy.

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Declarations

Conflict of interest The authors declare no competing interests.

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