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Sodium–glucose cotransporter inhibition in polycystic kidney disease: fact or fiction

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disease. Recent evidence suggests that the pathogenesis of ADPKD is a complex web of abnormal cellular processes including altered cell signaling, disordered cell metabolism, impaired autophagy, increased apoptosis, mitochondrial dysfunction and chronic inflammation. Sodium–glucose cotransporter (SGLT) inhibitors (SGLTi) reduce body weight, blood pressure and blood glucose levels, have kidney and cardiovascular protective activity, and have been reported to decrease inflammation, increase autophagy and improve mitochondrial dysfunction. We now review results from preclinical studies on SGLTi for ADPKD identified through a systematic search of the MEDLINE, Cochrane Library, Embase and PubMed databases. Potential underlying mechanisms for the conflicting results reported as well as implications for clinical translation are discussed, as ADPKD patients were excluded from clinical trials exploring kidney protection by SGLT2 inhibitors (SGLT2i). However, they were not excluded from cardiovascular safety trials or trials for cardiovascular conditions. A post-hoc analysis of the kidney function trajectories and safety of SGLT2i in ADPKD patients enrolled in such trials may provide additional information. In conclusion, SGLT2i are cardio- and nephroprotective in diverse clinical situations. Currently, it is unclear whether ADPKD patients may benefit from SGLT2i in terms of kidney function preservation, and their safety in this population remains unexplored. We propose a roadmap to address this unmet clinical need.

Keywords: apoptosis, autophagy, canagliflozin, dapagliflozin, polycystic kidney disease, SGLT inhibitors

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, which is characterized by the formation of numerous fluid-filled cysts primarily within the kidneys, often progressing to end-stage renal disease (ESRD) as renal cysts increase in number and size. Most cases are caused by mutations of either the polycystin-1 (*PKD1*) (75–85%) or polycystin-2 (*PKD2*) (15–25%) genes, the former having generally a worse prognosis [1, 2]. Sodium–glucose cotransporter-2 (SGLT2) inhibitors (SGLT2i) were introduced as antidiabetic drugs; however, more recently clinical trials have shown that they have heart and kidney protective effects in person with or without diabetes [3]. A systematic review of the literature was conducted to identify publications that detail the effect of sodium–glucose cotransporter (SGLT) inhibition in the treatment of ADPKD. The search was conducted in the following electronic databases: MEDLINE, Cochrane Library, Embase and PubMed. These electronic databases were searched on (until October 2021) using a structured search string, including the terms ADPKD and SGLT, ADPKD and SGLTi, PKD and SGLT, and PKD and SGLTi.

PATHOGENESIS OF ADPKD

The pathogenesis of ADPKD is a complex web of defective cellular processes including altered cellular signaling, increased apoptosis, impaired autophagy, mitochondrial dysfunction, increased aerobic glycolysis associated with hyperglycemia (Warburg Effect) and chronic inflammation [4]. Better understanding of these abnormal cellular processes has highlighted several treatment possibilities; however, few have fulfilled their initial promises and met the theoretical and pathophysiological expectations. The poor translation of preclinical animal studies to humans has several contributors, from animal models that do not reproduce the same molecular defect (*PKD1* or *PKD2* deficiency) to use of doses that cannot be achieved in human studies due to side effects. Thus, the treatment of ADPKD still remains a challenge revealing the unmet need for new therapeutic options, despite the availability of tolvaptan, a selective, competitive vasopressin receptor 2 (V2R) antagonist [5].

A diverse set of intracellular signaling pathways are dysregulated and contribute to the pathogenesis of ADPKD including the mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), vasopressin-mediated cyclic adenosine monophosphate (cAMP) and extracellular signal-regulated kinases (ERK) pathways [6–8]. Inflammation, mitochondrial dysfunction and metabolic reprogramming have also been held responsible for the formation and expansion of cysts. Finally, as for any chronic, slowly progressive form of CKD, the reduction in functional kidney mass may result in glomerular hyperfiltration and development of focal segmental glomerular lesions. The pathogenesis of ADPKD was examined and thoroughly explained in reviews and beyond the scope of the article [4].

THERAPEUTIC APPROACHES

Targeting cAMP signaling

Vasopressin binding to V2R induces cyst formation and transepithelial fluid secretion by increasing cAMP, especially in distal tubules [9]. Thus, suppressing vasopressin is a logical approach for reducing cysts within the kidneys. This may be achieved by daily water intake of 3–4 L over 24 h, although the feasibility and efficacy on ADPKD of long-term vasopressin suppression through increased water intake has not been demonstrated [10]. In addition, tolvaptan slows cyst and total kidney volume (TKV) growth and estimated glomerular filtration rate (eGFR) loss in persons with ADPKD [11–13]. However, tolvaptan is still an expensive medication, not available widely, and has significant side-effects (hepatotoxicity, polyuria) leading to intolerance and drug withdrawal in some patients. Additionally, residual risk for CKD progression remains unacceptably high.

Targeting mTOR signaling

Sirolimus and everolimus inhibit mTOR complex 1 (mTORC1) but not mTOR complex 2 (mTORC2). Although sirolimus and everolimus showed promising results in animal models, these findings unfortunately were not replicated in clinical trials [6, 14]. A new class of drugs, mTOR kinase inhibitors, directly binds to mTOR kinase and inhibits both mTORC1 and mTORC2. It was suggested that combined mTOR1 and mTOR 2 inhibitions may be more effective than solely inhibiting mTOR1 in PKD. PP242, an mTOR kinase inhibitor, reduced renal enlargement and cyst numbers in the Han:SPRD rat model of PKD. Compared with sirolimus, PP242 has a higher anti-proliferative effect and is a more effective mTORC1 inhibitor and less toxic on bone marrow, T and B cells [15, 16].

Targeting AMPK signaling

Metformin activation of AMPK and resulting inhibition of mTORC1 signaling lead to attenuation of PKD in the *Pkd1* mutant mice [17]. However, a phase II clinical trial of metformin for ADPKD identified several limitations such as gastrointestinal side effects and reduced bioavailability following a hepatic first-pass effect [18]. In this regard, the clinically maximum tolerable oral dose of metformin (i.e. 2.0 g/day) may still not be sufficient for AMPK activation in the kidney [19, 20]. Despite this, two ongoing phase 3 clinical trials are comparing metformin with placebo [NCT04939935: Implementation of Metformin theraPy to Ease Decline of Kidney Function in Polycystic Kidney Disease (IMPEDE-PKD), expected to be completed by 2026] or tolvaptan [NCT0376460: Metformin vs Tolvaptan for Treatment of Autosomal Dominant Polycystic Kidney Disease (METROPOLIS) expected to be completed by 2022].

Targeting fat metabolism

Hepatocyte nuclear factor 4a (Hnf4a) and the peroxisome proliferator–activated receptor-a (PPARa) are two major proteins responsible for decreased Fatty Acid Oxidation (FAO) in PKD [21]. Loss of Hnf4a function in PKD results in more severe cystic disease [21], while fenofibrate, a PPARa agonist, enhanced FAO and reduced cysts in an orthologous ADPKD model [22]. However, the clinical evaluation of this drug is limited by its potential to increase serum creatinine [23]. The mechanism is unclear and interference with creatinine secretion has been suggested. In any case, the increase in serum creatinine is rapidly reversible upon stopping fenofibrate and in fact, in a post-hoc analysis of a clinical trial, fenofibrate reduced albuminuria and slowed eGFR loss over 5 years in persons with diabetes [24].

Targeting energy metabolism

In ADPKD, impaired FAO is related to decreased mitochondrial Tricarboxylic Acid (TCA) cycle efficiency [25], rendering PKD cells mostly dependent on glucose and aerobic glycolysis instead of mitochondrial oxidative phosphorylation, known as the 'Warburg effect' [26, 27]. This shift generates 4 ATP and 2 lactate

molecules instead of 36 ATP molecules, and lactate is used to build macromolecules in highly proliferative cells such as cells lining cyst tubules [28]. Also, local hypoxia with mitochondrial dysfunction including mitochondrial fragmentation, swelling and reduction in mitochondrial DNA copy number were frequently observed in PKD [29–32]. Transcription and activity of glycolytic enzymes were increased and those of gluconeogenetic enzymes decreased in kidneys of Han:SPRD Cy/+ rats. Administration of 2-deoxyglucose (2DG), a glycolytic pathway inhibitor, decreased intrarenal lactate levels, ERK1/2 phosphorylation and cell proliferation, retarded cyst progression and attenuated renal functional decline in cystic rats [33, 34]. Thus, mitochondrial dysfunction with altered metabolic arrangements such as increased glycolysis and decreased oxidative phosphorylation appeared as the main characteristic features of PKD. However, therapeutic options are highly limited for adjustment of this altered metabolic state and mitochondrial dysfunction. SGLT2i seem like a promising agent for targeting energy metabolism and mitochondrial dysfunction.

Besides pharmacological therapies, some dietary strategies were also considered to slow down the progression of PKD such as daily energy restriction, time restricted feeding, intermittent fasting and ketogenic diets [35, 36]. Time-restricted feeding, compared with isocaloric ad libitum feeding, reduced blood glucose and increased ketogenesis, which inhibited renal cyst proliferation and growth. These findings are not merely due to time-restricted feeding since ad libitum administration of a ketogenic diet similarly inhibited renal cyst growth. In addition, acute fasting in rat, mouse and feline models of PKD induced significant apoptosis in cyst-lining epithelial cells but not in normal tissue, resulting in decreased renal cystic burden. These beneficial findings were all replicated with a ketogenic diet based on β-hydroxybutyrate; therefore, the metabolic state of ketosis seemed to be the crucial mediator of beneficial effects by inhibiting cyst growth and fibrosis via altering PKD-related signaling pathways like mTOR and STAT3 [27]. A recent retrospective case series also showed the feasibility of ketogenic diet for patients with ADPKD, concluding significant weight loss, improved blood pressure management and slight improvements in eGFR, with some safety concerns such as hyperlipidemia [37]. Overall, studies suggested that dietary restriction was beneficial for PKD progression by inducing ketosis, as renal cyst cells in PKD seem to be metabolically inflexible and thus unable to adapt to alternative fuel sources apart from glucose [27]. Moreover, several studies showed that ketogenic status is associated not only with better energy metabolism, but also with improved mitochondrial function and autophagy, which eventually contributed to controlling of inflammation and fibrosis [38].

These findings are supported by several studies that showed obesity and hyperglycemia were also correlated with faster disease progression in ADPKD [39–41], as well as functional and structural kidney damage in PKD [42]. Interestingly, one of the putative mechanisms of action of SGLT2i to promote heart and kidney protection is by increasing ketones such as β-hydroxybutyrate, which may also regulate histone post-translational modifications to regulate gene expression [43]. Thus, beneficial effects of SGLT2i seem closely linked to its efficacy on metabolism similar to the metabolic state of ketosis and β-hydroxybutyrate.

Targeting autophagy

Autophagy and autophagosome fusion with lysosomes (i.e. autophagic flux) are impaired in PKD [26, 44–46]. In a Pkd1 mutant zebrafish model, knockdown of autophagy protein Atg5 promoted cystogenesis, whereas treatment with the autophagy inducer Beclin-1 reduced cyst formation and growth [45]. However, a natural autophagy enhancer trehalose was ineffective in a Pkd1 mutant model [44]. Of note, mTORC-1 inhibits autophagy, and various rapalogs enhance autophagy and reduce cystogenesis in PKD [26, 45]. Although the drug arsenal for targeting autophagy was still under investigation, dietary interventions including a ketogenic diet were shown to improve parameters related to autophagy and improved inflammatory state with less fibrosis [36].

Targeting hypoxia-inducible factor

In ADPKD, cyst growth may compromise tissue perfusion and activate hypoxia-inducible factor (HIF), as HIF-1α and HIF-2α levels are associated with cyst burden [47]. Although, HIF-1α is thought to play an active role in the process of cyst expansion and pericystic angiogenesis, the HIF-1 inhibitor 2-methoxyestradiol (2ME2) had no significant effect on kidney volume or cyst volume density [46] and the impact of HIF stabilizers in clinical use or clinical trials for uremic anemia on ADPKD progression has not been adequately explored [48]. Even though they seemed to provide crucial benefits for PKD and anemia management of CKD patients, HIF-prolyl hydroxylase inhibitors are not currently favored due to a lack of data on their potential effects on cyst development or growth [47].

In addition to the aforementioned metabolic effects of SGLT2i, they have been proposed to play a beta-blocker-like effect in the kidneys, decreasing energy demand by proximal tubule cells, and may be expected to protect proximal tubule cells from a hypoxic environment [3]. Therefore, SGLT2i decrease renal hypoxia, enhance nutrient deprivation signaling, suppress HIF-1α and activate HIF-2α, which promotes erythrocytosis [49]. In a recent review of Patel and Dahl [47], effects of SGLT2i and HIF-prolyl hydroxylase inhibitors on ADPKD were compared in detail, suggesting that SGLT2i might provide a better alternative to tolvaptan rather than HIF-prolyl hydroxylase inhibitors for patients with ADPKD.

Targeting glomerular hyperfiltration

In ADPKD, higher baseline albuminuria was associated with faster eGFR loss [50]. Indeed, tolvaptan decreased albuminuria compared with placebo, independent of blood pressure. Treatment efficacy of tolvaptan on changes in TKV and eGFR was more readily detected in patients with higher albuminuria. Together with the observation that tolvaptan causes an early, reversible dip in eGFR, followed by a slower eGFR slope [51], similar to renin–angiotensin system blockers and SGLT2i [52], this observation supports a role of glomerular hyperfiltration of remaining nephrons in the progression of ADPKD. Indeed, in long-term studies, tolvaptan slowed eGFR decline, regardless of its impact on TKV, which was initially considered to be its mechanism of action [53]. This knowledge further supports the potential benefit of SGLT2i in ADPKD.

SGLT INHIBITION

SGLTs are a family of proteins mediating the transepithelial transport of glucose in the proximal tubule of nephrons and intestinal mucosa of small intestines. SGLT2 is a high-capacity, low-affinity transporter, which mediates the remaining 90% of glucose reabsorption in the proximal renal tubule [54, 55]. SGLT inhibition decreases Na^+–glucose reabsorption in the proximal tubule, thus decreasing energy needs, induces osmotic diuresis and increases distal tubule fluid rate. This leads to an increase

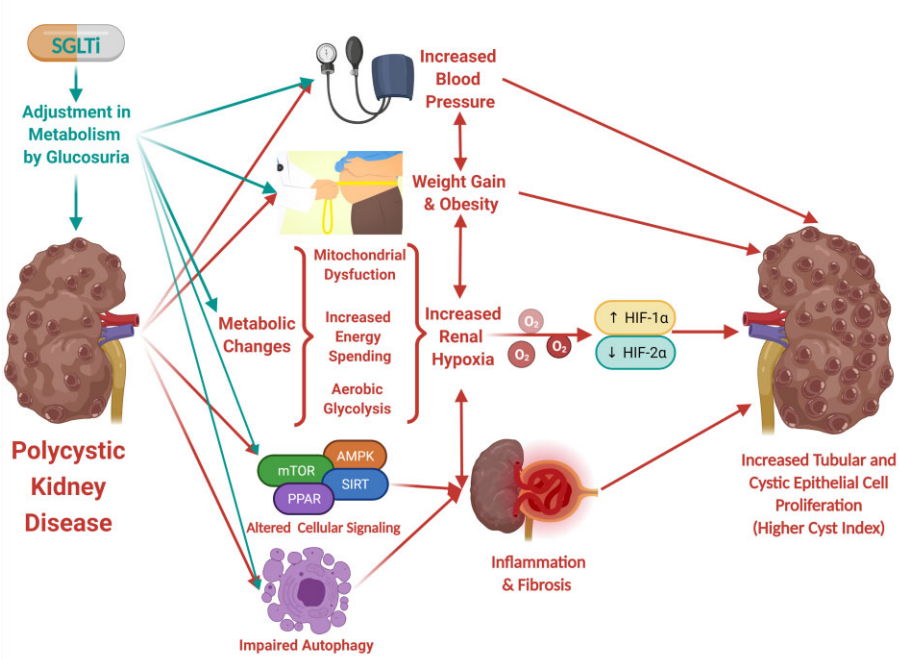

FIGURE 1: The suggested mechanisms of polycystic kidney disease (PKD) leading to higher tubular and cystic epithelial cell proliferation with higher cyst index are shown with red arrows. The possible beneficial effects of SGLTi on polycystic kidney disease (PKD) are shown with green arrows as they can interfere in multiple pathological processes of PKD by adjustments in metabolism via their glucosuric effects. SGLTi, sodium–glucose co-transporter inhibitor; HIF, hypoxia-inducible factor.

in afferent arteriolar tone because of tubuloglomerular feedback and thus corrects intra-glomerular hypertension and decreases hyperfiltration and its consequences such as albuminuria and metabolic overload of proximal tubules. Furthermore, SGLT2i have many other benefits such as reduction in HbA1c, blood pressure and weight reduction thanks to their glucosuric effect, which helps to get rid of excess glucose from body. Therefore, SGLT2 inhibition could be regarded as an antagonist of excessive carbohydrate consumption for the metabolism. Also, several studies have shown that SGLT2 inhibition has cardioprotective and nephroprotective effects in both diabetic and nondiabetic patients. Mechanisms contributing these benefits are still under investigation; however, switching metabolism to a ketotic state (e.g. increased β-hydroxybutyrate) by getting rid of excess glucose appears as the main mechanism. Importantly, an anti-inflammatory impact has been described for SLGT2i, as well as increased autophagy and improvement of mitochondrial dysfunction [38, 56]. Since PKD is associated with altered glucose metabolism, impaired autophagy, increased apoptosis and mitochondrial dysfunction, SGLT inhibition appears to be a very promising approach for the treatment (Figure 1). As the main beneficial mechanism of SGLT inhibition has similarity to a reduced carbohydrate diet, whether diet with reduced carbohydrate intake can achieve the same benefits also needs to be elucidated. While the impact of SGLT inhibition on PKD pathogenesis has been investigated over the last few years, studies are limited to preclinical models and results are conflicting. Below, we critically discuss the available and still needed studies.

SGLT INHIBITION IN PRECLINICAL PKD

SGLT inhibition has been tested in rat and murine models of PKD, but only the murine model was characterized by *Pkd1* deficiency as human ADPKD. Thus, the rat models may be suboptimal to extrapolate results to human ADPKD.

Rat PKD

Wang *et al.* studied the effect of phlorizin, an inhibitor of both SGLT1 and SGLT2, in PCKD Han:SPRD Cy rats over a 5-week period. PCKD Han:SPRD cy rats have a mutation in Anks6 (also called Pkdr1) which encodes SamCystin, a protein expressed in proximal tubules and glomeruli [57-58]. The mutation results in increased levels and mislocalization of SamCystin. These rats develop cysts exclusively in proximal tubules that become disconnected from these tubules. Phlorizin induced glycosuria and osmotic diuresis, increased creatinine clearance and decreased albuminuria. The kidney weight and cyst index were also lower in phlorizin-treated rats compared with placebo-treated rats. Moreover, phlorizin reduces cystic epithelial cell proliferation, assessed by Ki67 staining. In addition, phlorizin decreased ERK phosphorylation, which is increased in PKD, in a dose-dependent manner [58]. In another study with the same rat model, dapagliflozin for 5 weeks caused glycosuria and polyuria, increased creatinine and blood urea nitrogen (BUN) clearances, and decreased albuminuria despite failing to slow cyst growth and increasing kidney weight. Tubular epithelial cell proliferation, macrophage infiltration and interstitial fibrosis were similar in dapagliflozin- and vehicle-treated groups [54]. Kidney enlargement was attributed to widening of tubular lumen due to increased diuresis [54] and to tubular hypertrophy, thought to result from increased SGLT1-mediated glucose reabsorption in the S2 and S3 segments of proximal tubules [59]. Thus, in PCKD Han:SPRD rats with proximal tubular cysts, a dual SGLT1/SGLT2 inhibitor increased creatinine clearance, decreased kidney weight and cyst index while SGLT2i also preserved kidney function

deposit lack of an effect on cysts. Overall, the results support a protective effect of SGLT2 inhibition through mechanisms independent of cyst growth, likely dependent on interference with nonspecific mechanism of CKD progression. However, PCKD Han:SPRD Cy rats are not an optimal model of ADPKD as they involved a different protein target.

In PCK rats, dapagliflozin 10 mg/kg/day or vehicle was administered by gavage to 6-week-old male rats ($n = 9$ per group). PCK rats have a Pkhd1 genetic defect and are thus a model of autosomal recessive PKD [60]. They develop cysts in distal nephrons that remain connected to the tubule [61, 62]. Dapagliflozin increased glucosuria, urine output and creatinine clearance after 3 weeks; however, albuminuria was also increased 4-fold, suggesting that dapagliflozin induced hyperfiltration. Histological analysis and ultrasound showed a higher cyst volume and a 23% higher total kidney weight in rats treated with dapagliflozin. Renal cAMP content and Ki67 staining were similar between dapagliflozin- and vehicle-treated PCK rats [63]. Contrary to PCK rats, normal rats treated with dapagliflozin do not develop evidence of hyperfiltration and albuminuria [64, 65], so the findings in PCK rats were surprising [63]. Since PCK rats are a model of autosomal recessive PKD, the results are not directly relevant for ADPKD.

Murine PKD

Leonhard *et al.* [1] investigated the effect of salsalate (a nonsteroidal anti-inflammatory drug), metformin or canagliflozin on kidney cyst growth in an adult-onset mouse model of PKD caused by *Pkd1* deficiency. Salsalate or metformin plus salsalate increased kidney survival and reduced cystic kidney disease severity compared with untreated mutant mice. However, metformin did not add further protection to that afforded by salsalate alone and neither metformin nor canagliflozin alone was effective [1]. However, canagliflozin-treated mice were not studied in detail. Just kidney survival data were provided. Although at the end of the study kidney survival was similar to control mice, there was a lag time of 14 days (18%) between the development of kidney failure for the first control mouse and for the first canagliflozin mouse. More detailed studies are warranted. In this regard, this was an accelerated model of ADPKD in which both *Pkd1* alleles were inactivated, postnatally resulting in kidney failure at around Day 100 of disease, i.e. in very young mice, unlike human ADPKD for which only one *PKD1* allele is mutated leading to kidney failure at around age 65 years.

Understanding the results obtained in preclinical PKD

None of the preclinical studies was performed in an optimal model of human ADPKD. Overall, SGLT inhibition was protective in a rat model of proximal tubular cystogenesis but not in a rat model of human autosomal recessive PKD or in a murine model of *Pkd1* deficiency with a time course closer to the natural history of human autosomal recessive PKD than to the natural history of ADPKD. In any case, the authors of these manuscripts speculated for several potential explanations for the lack of efficacy. These include that osmotic diuresis induced by glycosuria may promote the dilation of distal tubules and linked cysts [63, 66] (Figure 1). However, human cysts are independent from tubules, and tolvaptan induced large diuresis volumes while being protective. Thus, this putative mechanism is not clinically relevant.

It has also been suggested that SGLT2 inhibition may increase vasopressin levels. In type 2 diabetic Goto-Kakizaki (GK) rats, after 8 weeks, ipragliflozin decreased body weight, serum glucose and systolic blood pressure, and increased fluid and food intake, urinary glucose and Na^+ excretion, urine volume and renal osmolar clearance, and most importantly urine vasopressin levels and solute-free water reabsorption (TcH2O). Urine vasopressin in ipragliflozin-treated rats was negatively and positively associated with fluid balance and TcH2O, respectively. Ipragliflozin increased expression of SGLT2, aquaporin 2 phosphorylated at Ser269, which is an important clue for strong vasopressin activity, and vasopressin V2 receptor. Thus, the osmotic diuresis induced by SGLT2 inhibition stimulated compensatory fluid intake and renal water reabsorption by increasing vasopressin levels to maintain body fluid volume [67]. Ho *et al.* [68] suggested that phlorizin could lead to increased endogenous vasopressin levels promoting distal tubular cyst growth, an effect that might not be seen in Han:SPRD rats as the cysts are almost exclusively of proximal tubular origin and unresponsive to vasopressin. Indeed, in type 1 diabetics, levels of copeptin, a more stable marker of vasopressin production, increased in response to empagliflozin under euglycemia and more so under hyperglycemia [69]. Under euglycemia, which would be the clinical conditions for ADPKD patients, the increase was modest (around 24%, to levels of 5.1 ± 2.8 pmol/L) and the clinical implications of this modest increase are unclear. However, in a further diabetic rat model, empagliflozin increased the expression in V2R but decreased protein and mRNA levels of AQP2, and this was associated with increased phosphorylation of AQP2 at S261, a marker of intracellular location, suggesting some blockade of V2R signaling [70]. Overall, the impact of SGLT2 inhibition on vasopressin responses and signaling under nondiabetic chronic conditions is not well understood and merits further clinical studies.

Finally, the impact of SGLT inhibition on PKD may depend on the specificity of SLGT inhibition. Cyst growth, renal function and albuminuria improved in Han:SPRD rats treated with phlorizin, which inhibits both SGLT1 and SGLT2 [58]. Thus, the result may be different with combined SGLT1 and SGLT2 inhibition as compared with SGLT2 inhibition alone, since combined complete SGLT inhibition is more powerful in terms of glycosuria [59]. In this regard, phlorizin is not in clinical use. However, diverse SGLT2i have different relative selectivity for SGLT2 and SGLT1, ranging from 20-fold (sotagliflozin) to 250-fold (canagliflozin) to over 1000-fold (in increasing selectivity order: dapagliflozin, ertugliflozin and empagliflozin, the latest with a selectivity of 2500-fold) [71].

SGLT2 INHIBITION IN CLINICAL ADPKD

Published clinical experience with SGLT2i and ADPKD remains limited or non-existent. Indeed, no publications were found in a PubMed search that also included the main SGLT2i (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin and sotagliflozin) on 9 October 2021. Unfortunately, patients with ADPKD were excluded from clinical trials assessing kidney protection as primary outcome in patients with or without diabetic CKD, such as A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (Dapa-CKD, NCT03036150), which recently demonstrated kidney protection conferred by SGLT2i in nondiabetic patients with CKD [72]. Furthermore, they were also excluded from EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin, NCT03594110) a further trial assessing kidney protection by SGLT2 inhibition in nondiabetic patients with CKD expected to be completed by 21 December 2022 [73]. Indeed, none of the ongoing 45 clinical

trials on PKD listed in ClinicalTrials.gov as of 4 October 2021 involves SGLT2 inhibition [74]. Thus, the clinical trial experience is and will remain limited for the foreseeable future. However, clinical trial NCT04680780 is exploring the feasibility of ketogenic dietary interventions and has a secondary endpoint of TKV. Promotion of ketogenesis is one of the putative kidney and cardioprotective mechanisms of action of SGLT2 inhibition [75]. However, ADPKD patients were not excluded from clinical trial assessing cardiovascular safety in persons with type 2 diabetes for assessing efficacy in cardiovascular conditions [76, 77]. Thus, a careful, targeted post-hoc analysis of several of these trials combined in search of persons with ADPKD that may have been enrolled because of coexisting diabetes or cardiovascular disease may provide further clues as to the safety and potential efficacy for kidney protection of SGLT2i in ADPKD.

SAFETY

Regarding safety, a main concern would be the risk of genitourinary infection, as an ascending infection affecting kidney cysts may have potentially severe consequences [78]. As ADPKD patients are more prone to urinary tract and cyst infections than the general population, the detrimental effects of possible infections including faster disease progression in ADPKD patients should be evaluated carefully in future studies. In any case, this information would only be hypothesis generating and would be useful to design further clinical studies as its post-hoc nature, presence of comorbidities and low patient numbers will prevent reaching definitive conclusions. In this regard, another drug with antidiabetic properties, the thiazolidinedione pioglitazone, was recently found to be safe in a phase 1b clinical trial for ADPKD, following reports of kidney protection effects in rodent PKD [79].

Another safety issue for using SGLT2i in ADPKD is their potential to exacerbation of hypovolemia, hypernatremia and acute kidney injury when combining with tolvaptan, which could prevent vasopressin-mediated water reabsorption [47]. Volume status of ADPKD patients under SGLT2i and tolvaptan treatment should be assessed carefully and their effects should be further explored in future studies.

Better understanding of the nature of ADPKD with its pathological processes is crucial for therapeutic selections in the future as some non-pharmacological dietary interventions like ketogenic diet, time-restricted diet, etc. could also provide beneficial effects to patients with ADPKD targeting altered metabolic state. Whether the usage of SGLT2i added more benefit to patients with ADPKD than other dietary interventions such as ketogenic diet or their beneficial effects are solely dependent on their glucosuria, and metabolic effects need to be elucidated in the future. Future studies and randomized controlled trials can be conducted to compare the feasibility, efficacy and the safety profile of SGLT2i and dietary intervention with a ketogenic diet based on β-hydroxybutyrate.

Table 1. Proposed roadmap to establish the safety and efficacy of SGLT2i for kidney and cardiovascular disease in persons with ADPKD

(A) Preclinical
1. Explore the efficacy and safety of SGLT2i in preclinical models of ADPKD that more closely resemble the kidney conditions: i.e. defective *Pkd1* gene and long natural history/and long-term SGLT2i treatment, leading to severe kidney disease well into adulthood.
2. Detailed characterization of the impact of SGLT2i on vasopressin and vasopressin signaling under nondiabetic conditions.

(B) Clinical. These sequential steps are proposed:
1. Create an SGLT2i-ADPKD task force.
2. Contact the leadership of all phase 3, large scale trials of cardiovascular safety or cardiovascular outcomes to extract, pool and analyze the safety and outcomes of persons with ADPKD that may have been enrolled in these trials.
3. Create a registry of ADPKD patients treated with SGLT2i for diabetes or cardiovascular conditions, assessing safety (urinary tract infections, copeptin, eGFR trajectories, TKV and albuminuria) as well as kidney efficacy (eGFR trajectories, TKV and albuminuria) outcomes.
4. Design short-term exploratory trials addressing the acute and short-term impact of SGLT2i on vasopressin, vasopressin signaling, eGFR and TKV, as well as safety.
5. Based on the result for steps 2 through 4, decide on the need, feasibility and design of larger, long-term phase 2 and phase 3 trials with endpoint efficacy on kidney protection or add warnings to drug labels regarding potential risks in ADPKD patients.

CONCLUSIONS

In conclusion, SGLT2i are currently established heart and kidney protective agents under diabetic and nondiabetic conditions. Thus, ADPKD patients might theoretically benefit from them in terms of kidney and/or heart protection and they may even be prescribed to the patients for cardiovascular conditions. However, clinical experience with SGLT2i is virtually nonexistent, as ADPKD patients were excluded from trials with kidney outcomes and whether they were enrolled in trials of cardiovascular outcomes is unclear. If ADPKD patients were enrolled in cardiovascular trials of SGLT2i, their outcomes have not been analyzed specifically. Preclinical studies had conflicting results because they were marred by the use of suboptimal animal models for a complicated human disease. In any case, there is basis for therapeutic concerns regarding the risk of infection and of increased vasopressin levels. Thus, a roadmap should be established aimed at establishing the safety of SGLT2i in persons with ADPKD, as they may need SGLT2i prescription for cardiovascular conditions, and to explore the eventual kidney benefit of this intervention (Table 1).

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AUTHORS' CONTRIBUTIONS

Contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: B.A., R.E.A., S.A., A.D., H.K., A.Y. Drafted the work or revised it critically for important intellectual content: B.A., R.E.A., A.O., A.C. and M.K.

CONFLICT OF INTEREST STATEMENT

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ETHICAL APPROVAL

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

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