

Role of sodium-glucose cotransporter 2 inhibition to mitigate diabetic kidney disease risk in type 1 diabetes

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ABSTRACT

Diabetic kidney disease (DKD) is a common complication of type 1 diabetes (T1D) and a major risk factor for premature death from cardiovascular disease (CVD). Current treatments, such as control of hyperglycaemia and hypertension, are beneficial, but only partially protect against DKD. Finding new, safe and effective therapies to halt nephropathy progression has proven to be challenging. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated, in addition to glycaemic lowering, impressive protection against DKD and CVD progression in people with type 2 diabetes. Although these beneficial cardiorenal effects may also apply to people with T1D, supporting data are lacking. Furthermore, the increased rates of euglycaemic diabetic ketoacidosis may limit the use of this class in people with T1D. In this review we highlight the pathophysiology of DKD in T1D and the unmet need that exists. We further detail the beneficial and adverse effects of SGLT2 inhibitors based on their mechanism of action. Finally, we balance the effects in people with T1D and indicate future lines of research.

Keywords: diabetic ketoacidosis, diabetic kidney disease, natriuresis, SGLT2 inhibitors, type 1 diabetes

DIABETIC KIDNEY DISEASE IN TYPE 1 DIABETES

Over 30 million people suffer from type 1 diabetes (T1D), increasing risk for early death mainly from cardiorenal disease [1, 2]. Despite advances in glycaemic and blood pressure control, a child diagnosed with T1D is expected to live up to 17 years less than non-diabetic peers [3–6]. The strongest risk factor for cardiovascular disease (CVD) and mortality in T1D is diabetic kidney disease (DKD) [7, 8]. DKD remains a common complication of T1D. Historically up to 40% of people with T1D had onset of elevated urinary albumin excretion and the

majority of these progressed to end-stage kidney disease (ESKD) within 10–15 years [9]. Although the cumulative incidence of DKD has been reduced with the achievement of intensive glycaemic control and renin–angiotensin–aldosterone system (RAAS) blockade, it remains a major morbid complication. In the Diabetes Control and Complications Trial (DCCT) and its observational follow-up study, the Epidemiology of Diabetes Interventions and Complication (EDIC) study, 25% of participants assigned to intensive therapy still developed elevated urinary albumin excretion during follow-up [10]. Current treatment of cardiorenal risk factors, such as control of hyperglycaemia and hypertension, is beneficial, but only partially protect against DKD. Additionally, while intensive glycaemic control is crucial throughout the disease duration, RAAS blockade may be more important in individuals with some degree of elevated urinary albumin excretion. Clinical trials in DKD in T1D have yielded disappointing results [11–18], potentially due to the lack of interventions at early stages of disease when the benefit is most likely. The recently published results from the Adolescent Type 1 Cardiorenal Intervention Trial demonstrated that the use of angiotensin-converting enzyme inhibitor and statin failed to change urinary albumin excretion over time in youth with T1D [19]. To effectively mitigate DKD risk in T1D, therapeutic strategies may have to target pathophysiology specific to T1D, and caution should be exercised when extrapolating trial data from people with type 2 diabetes (T2D). Thus identifying therapies to impede DKD in T1D remain a public health priority.

For people with T2D, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been introduced to improve hyperglycaemia. The glycaemic-lowering effects of SGLT2 inhibition are based on the fact that the kidneys approximately filter and completely reabsorb 180 g of glucose daily, an amount that is augmented in people with hyperglycaemia. The process of reabsorption is carried out by two transporters located in the

proximal tubule: the high-capacity, low-affinity SGLT2 and the low-capacity, high-affinity SGLT1, the functions of which are upregulated to facilitate increased glucose fluxes in the state of chronic hyperglycaemia. As non-specific SGLT inhibition by phlorizin provoked intolerable gastrointestinal side effects, more specific inhibitors were developed. These more specific SGLT2 inhibitors, initially brought to the market for glucose-lowering in people with T2D, now include canagliflozin, dapagliflozin, empagliflozin (EMPA), luseogliflozin and ertugliflozin. Sotagliflozin is different from other SGLT2 inhibitors, as it also inhibits intestinal SGLT1 activity and was specifically developed for people with T1D [20]. The glucose-lowering effects of SGLT2 inhibitors in people with T2D have been discussed in detail elsewhere [20], but it is important to realize that it is largely dependent on the filtered glycaemic load, which is determined by prevailing glucose concentrations (level of glycaemic control) and glomerular filtration rate (GFR). In T2D, SGLT2 inhibitors have also been shown to protect pancreatic β cells against glucose toxicity and preserve insulin secretory capacity, and murine models suggest that this may also hold true for T1D [21]. The SGLT2 inhibitors have received attention not due to their glucose-lowering efficacy, but through their remarkable cardiorenal effects. Indeed, SGLT2 inhibitors were shown to reduce cardiovascular risk (in people with previous CVD) and progression of DKD in several large trials, including Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), CANagliflozin cardioVascular Assessment Study (CANVAS), Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) (NCT01730534), Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) (NCT02065791) as detailed below. Several mechanisms of DKD progression overlap in people with T2D and T1D, and SGLT2 is a promising nephroprotective agent in people with T1D, supported by some recent data from the inTandem 1 and 2 trials (NCT02384941 and NCT02421510, respectively) [22]. However, there are also important differences that may limit generalization of T2D cardiovascular outcome trials (CVOTs) data to people living with T1D, as discussed below.

PATHOPHYSIOLOGY OF DKD IN T1D

The natural history of the pathophysiology of DKD

The natural history of DKD in T1D is characterized by progressive pathological changes that develop over a long silent period without clinical evidence of kidney dysfunction [23]. In fact, kidney biopsy data have established that structural defects precede functional impairment [24–26]. The International Diabetic Nephropathy Study (IDNS) demonstrated that the principal morphometric abnormalities of early DKD included increased glomerular basement membrane width and fractional volume of mesangium and mesangial matrix [23]. Furthermore, IDNS found these abnormalities as early as 2 years after T1D onset and structural defects advanced once increased urinary albumin excretion becomes detectable [23]. Strong and robust

relationships between glomerular structure and function have also been demonstrated in people with T1D [27, 28]. Notably, the histological features of DKD may differ in T1D and T2D. Compared with T1D, there appears to be greater structural lesion heterogeneity in people with T2D, for which reasons data should not be directly extrapolated [27–30]. The vast majority of studies have focused on the morphometry of the glomerulus, yet the proximal tubule may be equally if not more important in the initial onset of DKD [31]. In addition, there have been substantial advances and maturation of transcriptomic technologies that offer a platform to identify key genes and pathways involved in DKD in T1D. However, crucial components of the future success of these endeavours are deep phenotyping and access to renal tissue.

The sequence of progression of DKD in T1D has been proposed to start with hyperfiltration, resulting in glomerular injury followed by elevated urinary albumin excretion and progressive estimated GFR (eGFR) decline, eventually resulting in chronic kidney disease (CKD) and ESKD [32] (Figure 1). The data on hyperfiltration, however, are conflicting. For example, recent analysis of DCCT/EDIC data did not support hyperfiltration as an independent risk factor for the development of CKD and ESKD [33] and contradicts prior data from other groups [34, 35]. Although animal research and experimental models strongly support single-nephron hyperfiltration as an important early phenotype of kidney disease, whole-kidney GFR is measured in clinical research rather than single-nephron GFR. This is potentially problematic, as whole-kidney GFR is a product of the number of nephrons and the individual single-nephron GFR. Accordingly, to accurately diagnose single-nephron hyperfiltration from whole-kidney GFR, one relies on preserved nephron mass. However, nephron mass starts to progressively decline at ~25–30 years of age, and the decrease is faster in people with risk factors such as diabetes and hypertension [36]. Therefore there is likely a substantial portion of people with single-nephron hyperfiltration who are misclassified as being normofilterers based on their apparently normal ‘whole-kidney GFR’ in the setting of a reduced nephron mass. This is a recognized problem in nephrology, for which reason there are substantial efforts being made to non-invasively quantify nephron mass (e.g. cationic-enhanced magnetic resonance imaging) and thereby estimate single-nephron GFR [37].

This is also the reason it is preferred to study hyperfiltration as defined by ‘whole-kidney GFR’ in young people prior to progressive nephron loss, as there may be less heterogeneity in nephron numbers and therefore less misclassification bias. There is also no consensus on what rate of annual GFR loss constitutes rapid GFR decline. Annual declines >3 – 5 mL/min/ 1.73 m² or 3.3% have been proposed to predict DKD progression and mortality by different groups [34, 35, 38–40]. The implication of moderately increased albuminuria, previously known as microalbuminuria, has also been questioned over the past few years after the demonstration that it does not necessarily imply progressive nephropathy and regresses to normoalbuminuria in a significant proportion of people without therapy [41, 42]. However, in those with persistent moderately increased

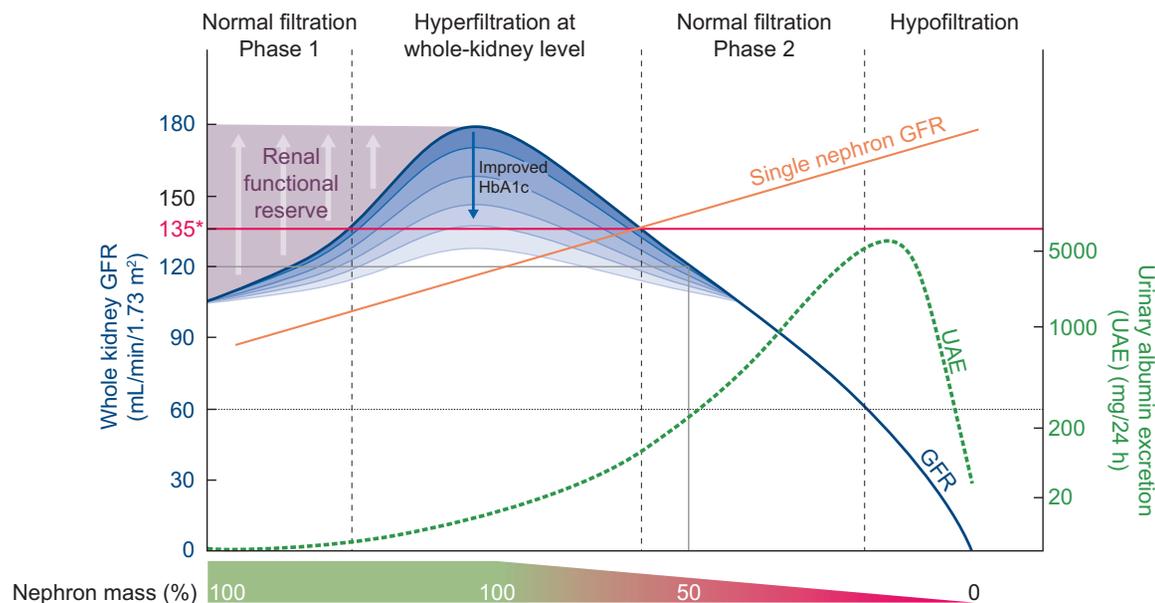


FIGURE 1: Progression of DKD in T1D. * whole-kidney hyperfiltration (≥ 135 ml/min/1.73m²)

albuminuria in the DCCT/EDIC study, the 15-year cumulative incidences of increased albuminuria (previously known as macroalbuminuria), impaired GFR and ESKD were 39, 19 and 7%, respectively [43]. Accordingly, persistent moderately increased albuminuria remains an important early phenotype of DKD. Further longitudinal research is needed to better understand the relationships between single-nephron hyperfiltration, rapid GFR decline and progressive nephropathy in people with T1D.

An energetic role of SGLT2 inhibition in DKD pathogenesis in people with T1D

The salutatory effects of SGLT2 inhibition in impeding DKD progression are incompletely accounted for by the modest improvements in HbA1c, weight and blood pressure. Metabolic and non-metabolic effects of SGLT2 inhibition have been proposed to explain the impressive cardiorenal benefits. The kidneys are highly metabolically active and are second only to the heart with respect to oxygen (O₂) consumption per tissue mass. To sustain this activity, the kidneys rely on various substrates to generate adenosine triphosphate (ATP), including citrate, glutamine, glucose and free fatty acids [44]. Early DKD is associated with an environment that exacerbates renal O₂ consumption in experimental models due to (i) elevated GFR and increased filtered sodium [34, 45, 46], (ii) increased activity of the Na⁺/K⁺ ATPase pump due to high tubular glucose and Na⁺ reabsorption and (iii) neurohormonal changes including increased vasopressinergic and RAAS activity [47–50]. In fact, animal models suggest that renal O₂ consumption is increased by 40% in all cortical segments and by 160% each in the S3 segment and medullary collecting duct in the setting of renal hypertrophy and hyperfiltration [51–55]. Furthermore, emerging animal data suggest that in diabetes the kidneys are unable to sufficiently compensate for the increased O₂ consumption due to the effects of insulin resistance and mitochondrial dysfunction on energy utilization [44, 56–58]. Data on renal O₂ consumption in DKD are currently limited to animal models. SGLT2

inhibition attenuates whole-kidney hyperfiltration in adults with T1D [59] and single-nephron hyperfiltration in animal models [60] and offers renal protection in adults with T2D and CKD [61]. In addition, adult data suggest that SGLT2 inhibition can improve insulin sensitivity [62]. Finally, animal data suggest that SGLT2 inhibition improves renal oxygenation and ameliorates renal hypoxia [63]. It is unclear whether the improved renal oxygenation in response to SGLT2 inhibition relates to natriuresis, as sodium excretion is not expected to be altered with prolonged treatment [64, 65], likely through compensatory sodium reabsorption at more distal tubular segments. However, alterations in the location of sodium reabsorption may affect the reuptake of other molecules, such as uric acid, that may also play a role in ATP consumption and generation [20, 66]. The consequences of SGLT2 inhibitor-induced alterations in sodium handling are not limited to renal energetics and include important non-metabolic changes in interstitial fluid volume, systemic haemodynamics and vascular function, which are all likely to contribute to the observed cardiorenal benefits [67, 68].

DIFFERENCES IN INTRARENAL HAEMODYNAMIC EFFECTS OF SGLT2 INHIBITORS IN PEOPLE WITH T1D AND T2D

Above, we described that several similarities exist between DKD in people with T1D and T2D. However, important differences should also be noted. In young adults with T1D, 8 weeks of SGLT2 inhibition resulted in afferent arteriolar vasoconstriction and a decrease in GFR in participants with baseline hyperfiltration [59]. The afferent arteriolar vasoconstriction is proposed to be mediated by increased distal sodium delivery and tubuloglomerular feedback. In contrast, recent data in older adults with T2D suggest that SGLT2 inhibition confers efferent arteriolar vasodilation with attenuated renal vascular resistance, possibly due to increased prostaglandin release [69]. The mechanisms underlying the different effects on intrarenal

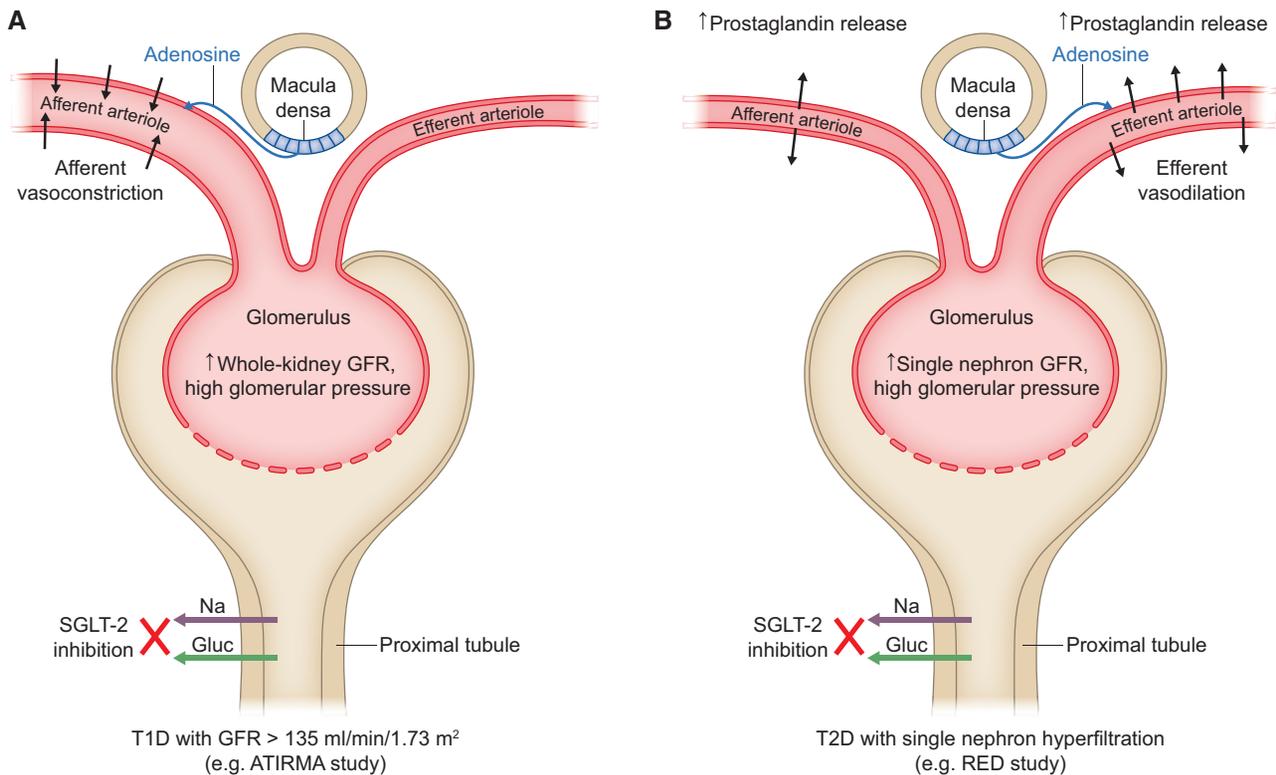


FIGURE 2: Intrarenal haemodynamic function changes in mechanistic trials with SGLT2 inhibitors in T1D versus T2D. The figure illustrates potential mechanisms explaining the differences observed in two mechanistic trials with SGLT2 inhibitor in young adults (~24 years of age) with T1D [ATIRMA study (NCT01392560)] and older adults (~63 years of age) with T2D [RED (NCT02682563)].

haemodynamic function remain incompletely understood but may relate to differences in factors governing arteriolar tone, including RAAS blockade and prostaglandin activity (Figure 2). For example, RAAS activation in DKD in T1D is associated with greater afferent arteriolar than efferent arteriolar vasoconstriction [70]. People with T1D are also known to have elevated circulating plasma cyclic guanosine monophosphate, which has been linked to greater efferent arteriolar tone and may explain the lack of efferent vasodilation in response to SGLT2 inhibition in people with T1D [71]. Furthermore, the role of renal vasoactive factors such as adenosine may be markedly different in the presence or absence of concurrent RAAS blockade, a group of drugs that is more commonly prescribed in adults with T2D. It also remains poorly understood whether these differences in intrarenal haemodynamic function relate to T1D versus T2D or rather are a function of age and diabetes duration. Future research should interrogate the mechanisms underlying the differences observed in people with T1D and T2D to better understand the role of SGLT2 inhibition in people with T1D. To better understand these differences, trials should enrol people with both T1D and T2D in adequate numbers to allow meaningful comparative analyses.

UNMET MEDICAL NEED IN T1D TREATMENT

Due to the deleterious effects of hyperglycaemia on microvascular and macrovascular outcomes, intensive insulin therapy, either by multiple insulin injections or via continuous subcutaneous insulin infusion, is employed in people with T1D

to achieve optimal glucose control (HbA1c <7.0% or 53 mmol/mol). Based on the data from the DCCT/EDIC, optimal glycaemic control was shown to impede the onset of vascular complications [72, 73]. In terms of DKD, in the DCCT/EDIC study, the development of macroalbuminuria was reduced by 54% (range 19–74) by strict glycaemic control, indicating the importance of glycaemic control for the kidney [73]. However, rigorous lowering of glycaemia by intensive insulin therapy, due to the absence of a feedback system, comes at the price of (severe) hypoglycaemia, particularly in the face of impaired awareness of hypoglycaemia in people with long-standing disease. Another undesired consequence of intensive insulin therapy is clinically significant weight gain, particularly in patients with frequent hypoglycaemia, and potentially insulin resistance, which has been causally linked to vascular complications [39, 74, 75]. Thus it is not surprising that many people with T1D fail to reach glycaemic targets, which represents a clear unmet medical need. Several efforts have been implemented to address these needs. First, pancreatic transplantation to restore islet cell function is sometimes combined with kidney transplant. Although pancreatic transplant can induce sustained diabetes remission, the surgery is associated with high mortality rates. Therefore ongoing research is focused on transplanting functional human pancreatic islets to people with T1D. In addition, current research aims to halt β -cell destruction through immunomodulatory therapies. Another approach is directed at improving insulin delivery, e.g. with closed-loop systems that allow glucose feedback on insulin delivery by reducing the risk for both hypo- and hyperglycaemia. Finally, strategies have

been pursued whereby additional (oral) pharmacotherapies are initiated to complement insulin therapy. Focusing on the latter, this has proven to be a challenging area. Studies with metformin [REMOVAL trial (NCT01483560)], the glucagon-like peptide-1 receptor agonist liraglutide [ADJUNCT ONE (NCT01836523)], the dipeptidyl peptidase-4 inhibitor sitagliptin and pramlintide showed overall modest benefits in adults with T1D when added to insulin therapy and could even increase adverse effects such as hypoglycaemia [76]. On the other hand, metformin therapy compared with placebo in adolescents with T1D was found to improve markers of CVD [77, 78]. The rationale for adjunct therapies in T1D is clearly evident based on the need for both glycaemic control and cardiorenal protection. However, the evidence to support the use of the above-mentioned therapies remains limited and future studies are needed.

GLYCAEMIC EFFECTS OF SGLT2 INHIBITION IN T1D

Recent studies have defined the effects of different SGLT2 inhibitors and dual SGLT1 and 2 inhibitors in people with T1D, adjunctive to standard of care insulin therapy (Table 1). In the DEPICT 1 trial (NCT02268214), dapagliflozin 5 and 10 mg once daily, compared with placebo, reduced HbA1c by 0.42 and 0.45%, respectively, at 24 weeks of treatment [79]; at Week 52, the differences remained -0.33% and -0.36% [80]. In the Empagliflozin as Adjunctive to InSulin thErapy trials, similar reductions were observed for 10 and 25 mg dosages (currently approved in T2D): -0.53% and -0.54% , respectively. The dosage of 2.5 mg yielded a placebo-corrected HbA1c reduction of -0.28% [81]. Finally, sotagliflozin reduced HbA1c by 0.36% and 0.41% in the inTandem 1 and inTandem 2 studies [82, 83]. Most patients in the trial programmes had reasonable glycaemic control prior to drug initiation due to insulin optimization during run-in and had preserved kidney function. It is important to emphasize that the achieved reduction in HbA1c was not accompanied by increased occurrence of (severe) hypoglycaemic episodes. Insulin reductions were seen across the trials and were mostly on the order of 10–15%. In glucose management of T1D, much attention has shifted from average glucose values as determined by HbA1c (an HbA1c value on target may include many hypo- and hyperglycaemic events that average out) to more complex measurements done by devices, such as flash glucose monitoring or continuous glucose monitoring (CGM). As such, the glycaemic parameter time in range (TIR), usually defined as glucose levels between 3.9 and 10.0 mmol/L, has received much attention. In the Dapagliflozin Evaluation in Patients With Inadequately Controlled Type 1 Diabetes trials, in 1591 participants with CGM analyses, dapagliflozin dosages increased TIR by 10–11% versus placebo [84, 85]. Furthermore, reductions in mean amplitude of glucose excursion (MAGE) were observed as well as 24-h mean glucose values, while values <3.9 mM were not increased. For sotagliflozin, a placebo-adjusted increase in TIR occurred in 5.4% for the 200 mg dose and 11.2% for the 400 mg dose [85]. Finally, EMPA 25 mg also showed increases of 10% TIR, while reducing glucose variability (glucose interquartile range and MAGE) [86]. The TIR percentages indicated above corresponded to ~ 3 h/day extra at the

highest dosages of each drug, without an increase in time for hypoglycaemia. It should be mentioned that the association between TIR and the development of microvascular complication is less well established as compared with the risk of high HbA1c levels and microvascular complications. However, two recent publications in people with T1D and T2D [87, 88] linked lower TIR to progression of retinopathy and albuminuria. With the increased use of sensor technology, more information will likely be available in the near future.

EXTRAGLYCAEMIC BENEFITS OF SGLT2 INHIBITION IN PEOPLE WITH T1D

The reason that SGLT2 inhibitors have received wide attention recently is not due to their glucose-lowering potential, as described above, but rather their impressive cardiorenal benefits. As mandated by the Food and Drug Administration (FDA), all trials with SGLT2 inhibitors have included placebo-controlled cardiovascular safety trials in the past couple of years. Unexpectedly, this drug class showed reductions in cardiovascular endpoints (i.e. the composite 3-MACE endpoint) in people with prior CVD, as reviewed extensively elsewhere [89, 90]. This improvement was driven by unprecedented reductions in hospitalization for heart failure [hazard ratios (HRs) ranging from 0.66 to 0.83]. Additionally, the composite endpoint of progression of nephropathy was improved (HRs ranging from 0.54 to 0.60), a finding that was confirmed in a study with DKD patients [61, 91, 92]. Of great importance, hard renal outcomes such as progression to ESKD were also reduced. The mechanisms behind the observed cardiorenal benefit continue to be incompletely understood. Although SGLT2 inhibitors modestly improve cardiovascular and renal risk factors such as blood pressure (~ 2 – 3 mmHg), body weight (~ 3 kg) and uric acid, it is unlikely that these factors completely mediate the observed benefits. Indeed, in a mediation analysis of the EMPA-REG OUTCOME trial, the largest predictor of favourable outcome was haematocrit, a marker of plasma volume. By inhibition of SGLT2, sodium and glucose reabsorption are concomitantly blocked. This in turn leads to temporary natriuresis, until sodium balance is restored by upregulation of other sodium transporters [64, 65]. However, the natriuresis-induced volume contraction is sustained over time. Thus alterations in sodium homeostasis and extracellular volume are thought to drive the observed cardiovascular benefit. At the kidney level, alterations in sodium handling may also drive the observed renohaemodynamic actions, where more distal sodium uptake could drive beneficial amelioration of hyperfiltration as detailed above.

The key question is whether the renal and cardiovascular benefits of SGLT2 inhibitors observed in people with T2D also apply to individuals with T1D. However, no such trials have been conducted, and it remains uncertain whether large-scale CVOTs will be performed in this population. At present, we have to carefully extrapolate T2D data and rely on biomarkers of cardiorenal health. In this regard, *post hoc* analyses from the EASE, DEPICT and inTandem trials may provide important insights. In a pooled analysis of the inTandem 1 and 2 studies, we found that sotagliflozin increased haematocrit by $\sim 2\%$, as well as serum albumin, confirming volume contraction [22].

Table 1. Studies with high-dose SGLT2 and dual SGLT1 and SGLT2 inhibitors in people with T1D

	Clinical Trials in People with Type 1 Diabetes							
	DEPICT 1	DEPICT 2	inTandem 1	inTandem 2	inTandem 3	EASE 1	EASE 2	EASE 3
Number of patients, ^a <i>n</i>	556	442	530	521	1402	37	487	486
Study drug	DAPA	DAPA	SOTA	SOTA	SOTA	EMPA	EMPA	EMPA
Drug high dose (mg)	10	10	400	400	400	25	25	25
Study duration (weeks)	52	24	52	52	24	4	52	26
Baseline HbA1c (%)	8.5	8.4	7.5	7.8	8.2	8.2	8.1	8.2
Change in HbA1c ^b (%)	-0.36	-0.42	-0.31	-0.32	-0.46	-0.49	-0.45	-0.52
Change in insulin TDD ^b (%)	~-10	-11.1	-12.6	-8.2	-9.7	-13	-12.9	-12.6
Change in body weight ^b (kg)	-3.6	-3.0	-4.3	-2.9	-3.0	-1.9	-3.6	-3.4
Change in time in range ^{b,c} (%)		+10.7	+10.4	+13.4	NA	+10.9	+12.5	+7.4
Ketoacidosis incidence rates, ^{d,e} <i>n</i>	13 versus 3	3 versus 0	11 versus 1	9 versus 0	21 versus 4	0 versus 0	16 versus 6	

High-dose treatment with SGLT1 or SGLT2 inhibitor: dapagliflozin 10 mg, EMPA 25 mg or sotagliflozin 400 mg.

^aIncluding placebo and high-dose SGLT1 or SGLT2 inhibitor treatment group.

^bPlacebo-adjusted.

^cCGM data for DEPICT-1 and DEPICT-2 were pooled for analyses.

^dIncidence rates for SGLT1/2 inhibitor versus placebo.

^eKetoacidosis incidence rates were pooled for EASE 2 and EASE 3 studies.

DAPA: dapagliflozin; SOTA, sotagliflozin; TDD, total daily dosage; NA, not available.

This may indicate similar cardiovascular mechanisms as in T1D adults. Salutary effects on blood pressure, body weight and uric acid were also reported. Given the role of elevated blood pressure, overweight and hyperuricaemia on hyperfiltration, reduction of these parameters could contribute to improved renal outcomes in adults with T1D. In addition, an early drop in eGFR similar to what has been shown in T2D was observed, and in those with albuminuria at baseline, a 40–60% attenuation of urinary albumin excretion was demonstrated [22]. These findings may implicate a reduction in glomerular pressure as a potential mediator of the nephroprotective effects consistent with the study by Cherney *et al.* [59]. Thus, while SGLT2 inhibitors have shown impressive beneficial effects on the cardiorenal axis in people with T2D, biomarkers suggest that these effects may also present in people with T1D. Given the burden of renal disease in people afflicted by T1D, this provides impetus for dedicated large-scale trials and cohort studies.

DIABETIC KETOACIDOSIS RISK IN T1D MECHANISMS: PREVALENCE AND IMPLICATIONS

SGLT2 and dual SGLT1 and 2 inhibitors are associated with several side effects. Most of the adverse reactions relate to their mode of action and are seen across the class. SGLT2 inhibitors induce glucosuria that makes the urine an attractive culture medium for bacteria, resulting in a slight increase in genitourinary infections. Most commonly observed infections are fungal infections of the genital skin (5–10% of treated women). However, for people with T1D, the most critical potential adverse effect concerns euglycaemic diabetic ketoacidosis (DKA). SGLT2 inhibitors increase ketonaemia, also in people with T2D. This is caused by reductions in plasma insulin concentrations or a reduction in insulin dosage and concomitant increments in glucagon concentrations. While ketone bodies have been hypothesized to explain beneficial cardiorenal effects of SGLT2 inhibitors, in people with T1D they increase the risk for acidosis. Due to apparent normoglycaemia secondary to

increased glucosuria, misdiagnosis of euglycaemic DKA continues to be a concern that could lead to delayed management. Risk factors for DKA in people with T1D have been identified and include large reductions in basal insulin therapy, insulin pump failure, reduced carbohydrate intake, use of alcohol, acute illness, vomiting and volume depletion/dehydration [93]. The percentage of DKA in the conducted trials in people with T1D was reported as 3.5% (4076 individuals treated with dual SGLT1 and 2 inhibitors) versus 0.6% (among 2362 placebo-treated individuals), which yields a 5.8-fold relative risk increase. As these numbers are derived from trials with motivated patients and expert physicians using careful surveillance and monitoring of ketonaemia (illustrated by very low DKA events in the placebo groups), it is plausible that the relative risk may be higher in clinical practice. An exception to these data concerns the novel low dose of EMPA (2.5 mg; currently not available), which demonstrated no increase in DKA rates, albeit at the expense of attenuated glucose-lowering actions. It should be mentioned that this low dose of EMPA is not yet available for clinical use.

A recently written consensus report written by international experts highlights the need for appropriate patient selection for SGLT2 inhibition and crucial knowledge available at the medical team. Finally, patients are required to measure ketones in addition to glucose levels and be trained on how to act upon increments, which is uncommon in clinical practice in most countries at present. Despite the usage of ketone metres, DKA rates were significant, which suggests that ketone body measurements are insufficient to mitigate DKA risk in people with T1D.

WEIGHING THE RISKS AND BENEFITS OF SGLT2 INHIBITORS IN T1D

The risk–benefit assessment of SGLT1 and 2 inhibitors in people with T1D remains challenging for health authorities and medical providers. In the USA, the FDA decided not to approve sotagliflozin as adjunctive therapy in people with T1D. In Europe, the European Committee for Medical Products for

Humans Use recommended the use of sotagliflozin and dapagliflozin for people with T1D, however, it was restricted to individuals with BMI >27 kg/m², based on *post hoc* analyses that showed these individuals might have a reduced risk to develop DKA. Based on preliminary data and biomarker analysis, low-dose SGLT2 inhibition may hold promise as an adjunctive therapy in people with T1D, especially those at high risk of DKD and CVD. However, CVOTs in people with T1D are needed to better understand the risk–benefit assessment, as data from people with T2D may not be generalizable to people with T1D. In fact, mechanistic studies suggest different effects of SGLT2 inhibition on intrarenal haemodynamic function in people with T1D versus T2D. T1D continues to be an exclusion criterion in the vast majority of pharma-sponsored clinical trials. However, the ongoing EMPA-Kidney includes a subset of people with T1D and DKD and may shed some important light. The medical community will likely remain sceptical until CVOTs in people with T1D data are available. Accordingly, future efforts should focus on designing a pragmatic CVOTs in people with T1D who are at high risk of DKD and CVD. Strategic partnerships between academia, pharma, organizations (e.g. Juvenile Diabetes Research Foundation, American Diabetes Association and European Foundation for the Study of Diabetes) and federal and state sponsors are needed to facilitate the development of pragmatic CVOTs in people with T1D. Real-world data from carefully designed studies could also help in this regard. This particularly holds true for the adverse effects. While efficacy can be accurately determined in randomized clinical trials, real-world evidence regarding ketoacidosis rates will provide crucial information on the risk of this drug class in people with T1D and will determine their future use.

CONCLUSION

Trials have established that SGLT2 inhibitors impede DKD progression in people with T2D. Although the mechanisms of nephroprotection remain uncertain, it may relate to improvements in renal haemodynamics, including reduced glomerular pressure, as well as improvements in renal risk factors such as blood pressure, hyperglycaemia, body weight and uric acid. However, DKD pathogenesis may be different in people with T1D compared with T2D. DKD in T1D may be characterized by distinct metabolic and renal haemodynamic perturbations, and data suggest that renal lesions from research biopsies also differ in people with T1D and T2D. Thus the question remains whether the renal benefits of SGLT2 inhibitors are also present in T1D. At present, we are unable to address this question due to the lack of dedicated trials in T1D, although certain renal biomarkers in non-dedicated renal studies as well as a mechanistic study focusing on renal haemodynamics suggest that SGLT2 inhibition may also confer nephroprotection in people with T1D. Renal trials investigating the effects of SGLT2 inhibitors in adults with T1D are now urgently needed. A major focus when designing these trials should be safety, as SGLT2 inhibitors, despite extensive surveillance measures, increase DKA risk. Without dedicated renal trials in people with T1D, the benefit–risk ratio cannot be meaningfully balanced for individual patients.

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AUTHORS’ CONTRIBUTIONS

The authors are fully responsible for all content and editorial decisions and were involved at all stages of manuscript development and have approved the final version.

CONFLICT OF INTEREST STATEMENT

P.B. has acted as a consultant for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Novo Nordisk and Horizon Pharma. P.B. also serves on the advisory board of XORTX. D.H.v.R. has acted as a consultant and received honoraria from Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk and Sanofi and has received research operating funds from the Boehringer Ingelheim–Eli Lilly Diabetes Alliance, MSD, AstraZeneca and Novo Nordisk.

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