Sodium-Glucose Cotransporter 2 Inhibition in Type 1 Diabetes: Simultaneous Glucose Lowering and Renal Protection?

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Introduction

In the effective management of type 1 diabetes mellitus, there exists a need to simultaneously meet glycemic targets while also targeting other factors that promote the development of complications. Intensive insulin therapy, the standard of care for glycemic control in type 1 diabetes, has profound beneficial effects on glycemia and complications risk that are marred by the amplification of weight gain and hypoglycemia. Novel consideration of adjunctive to insulin therapies—such as the coadministration of oral sodium-glucose cotransporter 2 (SGLT2) inhibitors—have the potential to improve glycemic control without dramatically

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- fonctionnement hémodynamique
- hyperfiltration
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- système rénine-angiotensine-aldostérone inhibition du SGLT2
- rétroaction tubuloglomerulaire
- diabète de type 1

A B S T R A C T

Diabetic nephropathy is the most common cause of end-stage renal disease requiring chronic dialysis or renal transplantation, resulting in high morbidity, mortality and societal costs to Canadians. Unfortunately, glycemic targets are often not achieved, and existing medications that block the renin-angiotensin-aldosterone system only offer partial protection against the development of renal and cardiovascular complications. As a consequence, in type 1 diabetes mellitus, 20% of patients treated with angiotensin-converting enzyme inhibition still have progressive nephropathy over 10 years. More recent work has suggested that blockade of renal sodium-glucose cotransport-2 (SGLT2) improves glycemic control and also reduces blood pressure, suggesting a potential for protective effects. Furthermore, in patients with type 1 diabetes, we have shown that SGLT2 inhibition reduces hyperfiltration and blood pressure, leading to renal and cardiovascular protection.

RÉSUMÉ

La néphropathie diabétique, la cause la plus fréquente d’insuffisance rénale terminale, nécessite la diâlyse à répétition ou la transplantation rénale entraînant une morbidité, une mortalité et des coûts sociaux élevés chez les Canadiens. Malheureusement, les cibles glycémiques sont rarement atteintes et les médicaments actuels qui bloquent le système rénine-angiotensine-aldostérone n’offrent seulement qu’une protection partielle contre l’apparition des complications rénales et cardiovasculaires. Par conséquent, lors de diabète sucré de type 1, 20 % des patients traités par l’inhibition de l’enzyme de conversion de l’angiotensine ont immuablement une néphropathie évolutive depuis plus de 10 ans. De plus récents travaux ont suggéré que le blocage du cotransporteur sodium glucose de type 2 (SGLT2) améliore la régulation glycémique et réduit également la pression artérielle, ce qui indique un potentiel d’effets protecteurs. De plus, chez les patients souffrant du diabète de type 1, nous avons montré que l’inhibition du SGLT2 réduit l’hyperfiltration, un facteur de risque de néphropathie diabétique et de dysfonctionnement vasculaire. Puisque la prévention primaire à l’aide des bloqueurs du système rénine-angiotensine-aldostérone ont été inefficaces lors de diabète de type 1, des études sur l’intervention précoce qui ciblent les autres mécanismes pathogéniques sont de la plus grande importance. L’inhibition du SGLT2, un nouveau traitement qui réduit simultanément l’hyperglycémie, l’hyperfiltration et la pression artérielle, s’avérerait sûre, et entraînerait une protection rénale et cardiovasculaire.
increasing hypoglycemia risk, while independently having salutary effects on weight, blood pressure and other metabolic parameters. Specifically, SGLT2 overactivity in diabetes has the problematic consequence of augmented glucose and sodium (Na) reabsorption by the nephron’s proximal tubular epithelial cells, which has 2 fundamental pathological effects: first, it maintains systemic hyperglycemia as a mechanism against osmotic diuresis of glucose; and second, the consequent decrease in distal tubular epithelium sodium delivery promotes renal hemodynamic dysfunction. This review places into context the early research findings of SGLT2 inhibition specifically in type 1 diabetes by describing the rationale and key research findings for its role, first, in the management of glycemic control and, second, for its role in renal protection.

**Physiology of SGLT2 in Health and Disease**

The precursor compound of modern SGLT2 inhibitors, phlorizin, was isolated from the bark of apple trees by French chemists in 1835 (1). Investigators subsequently observed that, similar to the signs and symptoms of diabetes in humans, phlorizin induced polyuria, polydipsia, polyphagia and weight loss in animals (2). Subsequent human studies demonstrated that phlorizin increases glycosuria in healthy persons (3). However, phlorizin is a nonspecific inhibitor of both SGLT1 and SGLT2 (2). As a consequence of SGLT1 inhibition, phlorizin also blocks intestinal glucose absorption, causing carbohydrate malabsorption, bacterial fermentation, gas and abdominal pain, which prevented further use of phlorizin in humans (2).

Subsequent modification of the chemical structure of phlorizin to produce C-aryl glycosides resulted in the development of selective inhibitors, which act in the proximal renal tubule to competitively inhibit sodium-glucose cotransport (4). SGLT2 is a high-capacity, low-affinity transporter located in the S1 and S2 segments of the proximal tubule responsible for 90% of glucose reabsorption in the kidney, whereas SGLT1 is a low-capacity, high-affinity transporter responsible for the remaining 10% in the S3 segment (5).

As reviewed elsewhere, SGLT2 has been estimated to be responsible for only 5% of total renal Na\(^+\) reabsorption under steady-state conditions in nondiabetes experimental models based on isolated renal micropuncture studies (6). However, in the context of hyperglycemia, the contribution of SGLT2 to renal Na\(^+\) reabsorption has been shown to be enhanced. Specifically, mRNA expression of SGLT2 and SGLT1 was increased by >20% in experimental models (6). Consequently, SGLT1/2 activity accounts for as much as 14% of total renal Na\(^+\) reabsorption in the setting of experimental diabetes (7), as compared with the 5% observed in controls. These findings were calculated based on the assumption that plasma Na\(^+\) concentration is 140 mmol/L and that the total proximal reabsorption of Na\(^+\) (including that mediated by SGLT1/2, net Na\(^+\) mass movement and Na\(^+\)–hydrogen exchange) is 75% of the filtered load in control rats and 85% in diabetic rats (8). This increased proximal reabsorption leads to 4 physiological consequences: 1) a marked reduction in distal Na\(^+\) delivery to the macula densa; 2) downregulation of tubuloglomerular feedback; 3) vaso-dilation of afferent arterioles, and 4) the glomerular hyperfiltration characteristic of diabetes (8,9).

From a therapeutic perspective, because of the marked increase in SGLT2 activity in diabetes, SGLT2 inhibition results in profound glycosuric responses (80 to 110 g per day) in type 2 diabetes (10) and type 1 diabetes (11–14). Experimental and human studies have taken advantage of the insulin-independent mechanism of action of SGLT2 inhibition to improve glycemic control and induce weight loss, primarily in type 2 diabetes (10). Animal studies and our pilot study in humans have also demonstrated positive effects on glycemic control, weight and arterial stiffness in type 1 diabetes (12,14,15). In addition to effects on glucose control, SGLT2 inhibition lowers blood pressure in patients with type 1 diabetes and type 2 diabetes, possibly because of diuretic effects and improved arterial compliance (12,13), as will be discussed in detail.

Based on these effects, clinical studies with SGLT2 inhibition in type 2 diabetes have focused on blood pressure and glucose lowering. However, SGLT2 inhibition also has potential renal protective effects in diabetes, possibly through modulation of tubuloglomerular feedback, thereby causing afferent vasoconstriction and reduced hyperfiltration in animals and humans (13,16). Therefore, based on a unique, insulin-independent mechanism of action, SGLT2 inhibition has the potential to improve both renal and glycemic outcomes in type 1 diabetes.

**Inhibition of SGLT2 Glycemic Control in Type 1 Diabetes**

Urgent need to determine novel approaches to address the problem of long-term adherence to glycemic control

Despite clear beneficial advances in insulin formulation and delivery—such as the development of basal and bolus insulin analogues, continuous subcutaneous insulin infusion and continuous glucose monitoring systems—patients with type 1 diabetes commonly fail to achieve optimal metabolic targets for preventing risk of complications (17,18). Although several factors may explain this gap between clinical research and practice, the fundamental barriers to successful intensification of insulin therapy are the risk and fear of hypoglycemia and weight gain (17,19). It is of critical importance to develop new therapies that improve glycemic control in patients with type 1 diabetes while simultaneously addressing the risk of hypoglycemia and weight gain and their negative metabolic consequences.

**Glycemic strategies using adjunctive-to-insulin therapy**

A number of strategies have recently been tested—or are being tested—in randomized controlled trials of adjunctive-to-insulin therapies to help address this need (20). These include metformin therapy (21), thiazolidinediones (22), alpha-glucosidase inhibitors (23) and incretin therapies, which include amylin analogues (24,25) dipeptidyl peptidase-4 (DPP-4) inhibitors (26) and glucagon-like peptide–1 (GLP-1) receptor agonists (27,28).

Substantial insulin dose reductions and putative effects on cardiovascular risk attributable to adjunctive-to-insulin metformin therapy have been observed in several studies and summarized in systematic review (21). Owing to these findings, the clinical impact of metformin is currently being pursued in a multicentre clinical trial (Reducing With Metformin Vascular Adverse Lesions in Type 1 Diabetes [REMOVAL], www.clinicaltrials.gov NCT01483560) investigating the effect of 3 years of metformin therapy on a cardiovascular disease surrogate, carotid intimal media thickness, in 500 overweight subjects. Alpha-glucosidase inhibitor trials have shown modest glycated hemoglobin (A1C) reductions in subjects with type 1 diabetes (23), whereas trials of insulin sensitization by way of thiazolidinediones have implied concerns over adverse effects such as edema, weight gain and possible accelerated decline of insulin production (22,29). Amylin analogue therapy with subcutaneously administered pramlintide has long been approved by the US regulatory authority. A 1-year double-blind, placebo-controlled, randomized clinical trial involving 480 subjects with type 1 diabetes demonstrated substantial benefits for glycemic control and weight reduction (24), but it should be noted that in postmarketing monitoring, hypoglycemia risk arose as a concern that may have limited its systematic adoption into clinical practice.

Although the effect on glycemic control by way of incretin-based therapy with the DPP-4 inhibitors may be modest, the effect in
short-term studies was significant and associated with reduction in insulin requirements without weight loss (30). The impact of the glucagon-related peptide-1 receptor agonist liraglutide in a short-term pilot study (38) has influenced the design and initiation in 2013 of a 1400-subject randomized clinical trial (Efficacy and Safety of Liraglutide as Adjunct Therapy to Insulin in the Treatment of Type 1 Diabetes [ADJUNCT ONE], www.clinicaltrials.gov NCT01836523) of liraglutide versus placebo for the 1-year effect on the change in A1C. The dramatic impact of leptin analogues on glycemic control in murine models (31) has led to a proof-of-concept, open-label trial in humans (Effects of Metreleptin in Type 1 Diabetes Mellitus, www.clinicaltrials.gov NCT01268644).

Although limited as to the number of large-scale randomized clinical trials, the concept of additive-to-insulin therapy for type 1 diabetes has long been investigated and has now culminated in intensified clinical trial effort.

**Putative novel benefit of additive-to-insulin SGLT2 inhibitor therapy**

Selective inhibition of the renal proximal tubular SGLT2 lowers blood glucose through the inhibition of renal glucose reabsorption (10). Although oral agents in the SGLT2 inhibitor class are at this time approved by European and US regulatory agencies for use exclusively in type 2 diabetes, there are several reasons that they may be useful as additive-to-insulin therapy for patients with type 1 diabetes. First, the mechanism of glucose disposal is independent of insulin action (15,32). Second, the glucose disposal represents a caloric loss that may have consequent salutary effects on weight gain (13). Third, SGLT2 inhibition promotes mild diuresis and blood pressure lowering, and may further provide renal protection through a reduction in intraglomerular pressure (13).

The beneficial effects of SGLT2 inhibitors on glycemic variables and weight loss in patients with type 2 diabetes have been clearly demonstrated by randomized clinical trials as monotherapy and in combination with other oral hypoglycemic agents (10). Conceptually, the use of SGLT2 inhibitors in the context of type 2 diabetes treated without insulin or sulfonylureas is considered to have low hypoglycemia risk in view of the mechanisms of action that are independent of insulin secretion and independent of peripheral insulin sensitization. However, a key finding from the type 2 diabetes literature was the efficacy and safety of an SGLT2 inhibitor as additive therapy to insulin at doses of at least 30 units per day—and in one study, even higher (33)—with or without other oral hypoglycemic agents (34).

In a 24-week study, dapaglizofin was associated with incremental A1C lowering of 0.4% compared with that of placebo and a durable A1C reduction of 0.54% compared with placebo at the end of an extension phase, which ended at 48 weeks and during which hypoglycemia rates were not increased in either study phase (34). Durable effect was observed in a similar 78-week trial of empaglizofin in which a 0.6% A1C reduction was observed (33). Although earlier work of add-on therapy to insulin for type 2 diabetes patients included a 50% total daily insulin reduction at initiation of SGLT2 inhibitor, the procedures in the more recent trial (33,34) did not include initial insulin dose adjustment, and smaller mean increases in total daily insulin were observed in the active therapy groups compared with placebo.

In addition to these results of studies with SGLT2 inhibition in type 2 diabetes subjects for whom hypoglycemia risk was not incrementally higher, several principles support low hypoglycemia risk in type 1 diabetes. First, the insulin-independent mechanism of action of empaglizofin likely explains the reduction in hypoglycemia risk. Second, previous human studies have demonstrated the protective effect of a physiological decline in glomerular filtration rate in the face of hypoglycemia that results in suppressed urinary glucose excretion during hypoglycemia. This effect is hypothesized to result from the sympathetic nervous system activation associated with hypoglycemia and the subsequent renal vasoconstriction that reduces renal blood flow and urinary glucose excretion (35). Third, the quantity of glucose delivered to the proximal tubule is dependent on the concentration of plasma glucose. In the setting of a declining plasma glucose level, less glucose is delivered to the proximal tubular epithelium, which in turn may decrease the hypoglycemic effect of the SGLT2 inhibitor (3). Fourth, the increased urinary glucose excretion associated with empaglizofin may be associated with a compensatory increase in hepatic gluconeogenesis, which, in turn, appears to be associated with a reduction in hypoglycemia in persons with type 2 diabetes (36).

**Studies of SGLT2 inhibition in type 1 diabetes**

Until recently, the clinical research experience of SGLT2 inhibition in the setting of type 1 diabetes was extremely limited. In combination with low-dose insulin in animal models, empaglizofin and other nonselective SGLT1/2 inhibitors provided similar glucose-lowering efficacy compared with high-dose insulin (15,37,38). Knowledge of the efficacy of SGLT2 inhibition in humans with type 1 diabetes has until recently been restricted to a single study that examined the effect of remoglizofin on plasma glucose in a dose-escalating study of 10 insulin pump users over 10 hours after a 75 g oral glucose challenge (32). In that study, subjects continued to receive basal insulin and were then randomly allocated on separate days to receive prandial insulin or placebo or 1 of 3 doses of remoglizofin before the oral glucose tolerance test. Although the mean glucose profiles were not as optimal as with prandial insulin, use of remoglizofin compared with placebo was associated with substantial improvements in the glucose profile over 10 hours (32).

The longest experience with SGLT2 inhibition in type 1 diabetes to date is that observed in a recently published single-arm, open-label study designed with the primary objective of investigating renal hemodynamic effects of SGLT2 inhibition (39). Here, we describe the findings and implications of the study in detail (Table 1). In that study, we sought to determine the feasibility, safety and efficacy of 8 weeks of treatment with empaglizofin (25 mg once daily) on glycemic parameters in patients with type 1 diabetes receiving intensive basal-bolus insulin therapy and optimized care. The SGLT2 therapy was found to be well tolerated and had salutary effects on glycemic control and anthropomorphic measures compared with a 2-week placebo run-in period. Glycemic control, represented by A1C as well as fasting and nonfasting capillary blood glucose levels were significantly improved despite substantial reductions in total daily insulin doses and increased

<table>
<thead>
<tr>
<th>Variables</th>
<th>Glycemic parameters</th>
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<tr>
<td>Glycated hemoglobin: improvement of 0.4% over 8 weeks</td>
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<tr>
<td>Fasting glucose: improvement of 2.0 mmol/L over 8 weeks</td>
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<tr>
<td>Hypoglycemia incidence: ~50% reduction in events per patient per day over 8 weeks</td>
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<tr>
<td>Total daily insulin: ~20% reduction in units per day over 8 weeks</td>
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<tr>
<td>Basal insulin: ~25% reduction in units per day over 8 weeks</td>
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<tr>
<td>Prandial insulin: no specific significant reduction over 8 weeks</td>
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<tr>
<td>Carbohydrate intake: ~30% increase in grams per day of carbohydrate intake</td>
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<td>Urinary glucose excretion: ~6-fold increase in grams per day</td>
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<td>Anthropomorphic measures</td>
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<tr>
<td>Weight: 2.6 kg weight loss over 8 weeks</td>
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<tr>
<td>Waist circumference: 3.8 cm loss over 8 weeks</td>
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carbohydrate intake. Specifically, A1C decreased from 8.0%±0.9% to 7.7%±0.9% at week 4 and 7.6%±0.9% at week 8 (mean baseline to week 8 decrease 0.4%, p < 0.0001). To determine whether this A1C improvement was primarily observed in subjects with the highest levels at baseline, we undertook a stratified analysis (Figure 1). In the 22 subjects with baseline levels ≥8%, the A1C declined from a level of 8.7%±0.6% to 8.3%±0.8% (p = 0.001). In the 18 subjects with baseline levels of <8%, A1C declined from 7.2%±0.4% to 6.9%±0.5% (p = 0.002). The total daily insulin doses decreased from 54.7±20.4 to 43.0±22.9 units, representing a decrease exceeding 20%, and was represented primarily by basal insulin reduction. Although a mechanism could not be explained by that study, the amount of daily carbohydrate consumed increased over the course of the study. Further benefits were a decline in the frequency of hyperglycemia, and substantial short-term improvement in weight (a loss of nearly 3 kg over 8 weeks) and waist circumference (a decrease of nearly 4 cm over 8 weeks). The study supported the hypothesis that adjunctive-to-insulin therapy with SGLT2 inhibition, through the caloric loss induced by exaggerated urinary glucose excretion, may provide an additional strategy to therapeutic lifestyle interventions for maintenance of healthy weight in type 1 diabetes patients.

In that study, we were concerned with initiating outpatient therapy with SGLT2 inhibition without insulin dose reduction, particularly in light of data that suggested a mean daily excess urinary glucose excretion approximating 80 g to 90 g was associated with empagliflozin (40)—in the range of one-third of total daily carbohydrate intake for most patients with type 1 diabetes. Therefore, our study protocol included a 30% reduction in prandial insulin, and, as an additional safety measure for preventing hyperglycemia, we implemented a similar basal insulin reduction at the initiation of study drug. In view of the low hypoglycemia risk, we recognize that a smaller and individualized reduction in insulin doses at initiation of study drug may have provided greater glycemic efficacy, particularly in view of the finding that the mean total daily insulin dose was approximately 20% lower at end of treatment rather than the 30% reduction made according to our protocol at drug initiation. The finding that basal insulin reduction was maintained throughout the study in association with major improvements in fasting glucose levels reinforced the message that basal insulin dose reductions should be considered for future investigation of empagliflozin in type 1 diabetes. However, the development of clinical protocols to determine the magnitude of individualized basal and prandial insulin dose adjustment at the initiation of empagliflozin and other SGLT-2 inhibitors requires further study.

Two subjects were not included in the efficacy analyses of the pilot study as they were withdrawn after the early occurrence of diabetic ketoacidosis, the one due to gastroenteritis and the other due to insulin pump failure. Although both subjects had initial reduction of total daily insulin dose by 30% on the first day of empagliflozin therapy according to protocol, according to the investigators’ judgement in response to capillary glucose readings on the first and second days of therapy, their insulin doses were subsequently more aggressively reduced to 70% and 50% of their pretreatment levels. Both patients fully recovered from the diabetic ketoacidosis episodes. Although the presentation of the 2 cases of diabetic ketoacidosis did not imply a causal relationship between empagliflozin and ketoacidosis in that the episodes occurred in the presence of clear clinical precipitants, we considered the possibility that empagliflozin may have modified the clinical presentation. Specifically, both patients had nausea and plasma glucose concentrations that could be interpreted as lower than typically associated with diabetic ketoacidosis. Although speculative, increased urinary glucose disposal induced by the initiation of SGLT2 inhibition may be akin to the disposal observed in fasting, prolonged activity or pregnancy, in which cases of atypically lower plasma glucose concentration have been observed (41,42).

Although the existing clinical studies support the hypothesis that adjunctive-to-insulin use of empagliflozin in type 1 diabetes has substantial beneficial effects on glycemic control, hypoglycemia prevention and weight, confirmation requires a future randomized and blinded clinical trial of longer duration. Also, further work is required to better explain the cause of the observed compensatory increase in carbohydrate intake associated with an SGLT2 inhibitor, and specifically, whether increased urinary glucose excretion can stimulate this compensatory increase in food intake. Finally, although explained by clear precipitants other than the use of an SGLT2 inhibitor, in addition to further development of recommendations for individualized insulin dose adjustment and titration, the risk of ketosis should be carefully monitored in future trials.
Inhibition of SGLT2 as Renal Protective Agent in Diabetic Nephropathy

Hyperglycemia, hyperfiltration, neurohormonal activation and SGLT2 in diabetes

The elevated tubular sodium delivery and GFR through TGF is silenced when diabetes occurs (B). Under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT-2 (GFR) by modulation of preglomerular arteriole tone. In cases of conditional increases in GFR, the macula densa within the juxtaglomerular apparatus senses an increase in distal sodium-glucose cotransport-2 (SCLT-2) inhibition (10). Under physiological conditions, tubuloglomerular feedback (TGF) signalling maintains stable glomerular sorption of sodium (Na$^{+}$) in intact organs, human studies have used direct measures of GFR as surrogates for intraglomerular pressure (13). Similar to observations in animals, hyperfiltration is an independent risk factor for the initiation and progression of nephropathy in type 1 diabetes and type 2 diabetes (45,46). Furthermore, as in animal models, there is clear evidence that factors that reduce intraglomerular pressure through neurohormonal blockade, such as RAAS inhibitors, are renal protective in humans.

Neurohormonal hypothesis for hyperfiltration

What causes RAAS activation in type 1 diabetes? Persistent hyperglycemia appears to play a primary role in this process through increased renin and angiotensinogen gene expression and activity, resulting in efferent renal arteriolar vasoconstriction (47). That, in turn, leads to increases in intraglomerular pressure and single nephron GFR, thereby promoting hyperfiltration and progressive glomerular injury in animal studies (48).

In clinical practice, RAAS inhibition is the cornerstone of renal protective therapy for type 1 diabetes. Unfortunately, we have demonstrated that angiotensin-converting enzyme (ACE) inhibition reduces, but does not normalize hyperfiltration in patients with type 1 diabetes (49). That is important because hyperfiltration has been implicated in the initiation and progression of diabetic nephropathy in animal studies and, in humans, hyperfiltration independently predicts adverse outcomes, including the development of microalbuminuria, loss of renal function and hypertension (45,46). Perhaps as a consequence of this incomplete effect on hyperfiltration, RAAS blockers only partially reduce chronic kidney disease risk in diabetes (50,51). Whatever the underlying mechanism, primary prevention strategies with ACE inhibition for patients with uncomplicated type 1 diabetes provide limited renal protection, highlighting the urgent need for a new approach to renoprotection in early type 1 diabetes. Based on the failure of RAAS inhibition to fully attenuate renal hyperfiltration or the development of nephropathy in patients with diabetes, it is of the highest importance to block alternative pathogenic mechanisms linked with diabetic nephropathy, including renal tubular factors.

Tubular hypothesis for hyperfiltration

Renal tubular factors have been strongly implicated in the pathogenesis of diabetic renal disease. According to the tubular hypothesis, tubuloglomerular feedback mechanisms contribute to the early pathogenesis of diabetic nephropathy through effects on renal hemodynamic function (52). The tubular hypothesis is based on the observation that diabetes-related hyperglycemia increases proximal tubular glucose delivery, resulting in augmented proximal tubular glucose reabsorption along with Na$^{+}$ by SGLT2. Furthermore, diabetes is associated with increased SGLT2 mRNA expression and activity (53). As a result, distal Na$^{+}$ delivery to the macula densa decreases, which is sensed as a reduction in effective circulating volume by the juxtaglomerular apparatus, leading to afferent renal vasodilatation, increased intraglomerular pressure and renal hyperfiltration (Figure 2). High intraglomerular pressure is associated with initiation and progression of nephropathy and agents that reduce intraglomerular pressure, such as ACE inhibitors and angiotensin-II receptor blockers, are renal protective (54). Although experimental data and our observations...
of patients with type 1 diabetes suggest that SGLT2 inhibition reduces hyperfiltration, the effect of SGLT2 inhibition on future renal disease risk is unknown. In summary, neurohormonal and tubular mechanisms contribute to renal hyperfiltration, which is present in approximately 50% of patients with type 1 diabetes. Hyperfiltration is clinically relevant owing to its association with the initiation and progression of diabetic nephropathy (45,46). With the emerging availability of pharmaceutical agents that block both neurohormonal and tubular pathways leading to hyperfiltration, it will be important to determine whether SGLT2 inhibition with and without RAAS blockade leads to additive, protective renal hemodynamic effects that have thus far only been demonstrated in animals (55–59).

**Effect of SGLT2 inhibition on renal hemodynamic function in diabetes**

**Animal studies**

To target tubuloglomerular feedback mechanisms that promote renal disease progression in diabetes, experimental animal models have used nonspecific inhibitors, such phlorizin, as well as specific SGLT2 inhibition (60,61). Phlorizin is renal protective in animals, resulting in decreased hyperfiltration, proteinuria and renal hypertrophy (9,60). The clinical relevance of these observations has been unclear, however, because phlorizin cannot be used in humans. Subsequent animal studies with selective SGLT2 inhibitors have suggested they could have significant clinical benefits for diabetes, since they have been shown to have similar beneficial effects on markers of diabetic nephropathy, including reductions in hyperfiltration, proteinuria, glomerular hypertrophy and mesangial expansion as well as in levels of inflammatory mediators such as reactive oxygen species and interleukin-6 (58–59). Consistent with the pharmacological effects of SGLT2i, SGLT2 knock out models exert similar effects on renal hemodynamic function, characterized by a significant reduction in hyperfiltration (62).

Despite empirical evidence showing renal protective effects of SGLT2 inhibition in animals, the signalling mechanisms that link SGLT2 inhibition with reduced hyperfiltration remain incompletely understood. As reviewed elsewhere, the macula densa–derived vasoconstrictor adenosine is involved in normal physiological mechanisms that regulate renal Na⁺ handling (63). However, decreased adenosine bioactivity has also been implicated in the pathogenesis of hyperfiltration related to tubuloglomerular feedback. Furthermore, adenosine may mediate the renal hemodynamic effect of SGLT2 inhibition. In brief, SGLT2 inhibition therapy increases distal tubular Na⁺ delivery. The resulting increase in intracellular Na⁺ transport into macula densa cells across sodium-potassium-2-chloride channels requires macula densa cell membrane depolarization. Depolarization to facilitate increased Na⁺ reabsorption requires energy, resulting in adenosine triphosphate breakdown to adenosine, which is released in a paracrine fashion, thereby causing afferent vasconstriction and a decline in hyperfiltration (7). This tubuloglomerular feedback effect is mediated by adenosine through adenosine A1 receptors on afferent arteriolar vascular smooth muscle cells, leading to vasoconstriction (63). Based on these principles, it is therefore not surprising that diabetic A1 receptor knockout animals that cannot adequately constrict the afferent arteriole exhibit augmented hyperfiltration, leading to exaggerated glomerular injury (63). From a therapeutic perspective, these experimental observations support the notion that increased renal adenosine bioactivity should reduce hyperfiltration in diabetes, thereby providing renal protection. The effect of adenosine on afferent arteriolar tone and tubuloglomerular feedback has been studied in animals, but the relevance and effect of SGLT2i on adenosine in humans has not been investigated.

**Human studies**

The effects of SGLT2 inhibition on glycemic control, blood pressure and anthropomorphic outcomes have been well documented in patients with type 2 diabetes (16,64), and similar beneficial effects on glycemic control, weight and blood pressure occur in type 1 diabetes (32). Furthermore, SGLT2 inhibition treatment significantly reduces renal hyperfiltration by an amount that is similar to that observed during therapy with ACE inhibition (49). In light of the poor prognosis associated with hyperfiltration in patients with type 1 diabetes and type 2 diabetes (45,46) and the renal protective effects of SGLT2 inhibition in experimental models of diabetes (56), our findings in patients with type 1 diabetes suggest that SGLT2 inhibition may promote a protective decrease in intraglomerular pressure (55,57,60).

Despite what is known from animal studies and our human studies in type 1 diabetes, data regarding the longer-term influence of SGLT2 inhibition on renal function are available only for patients with type 2 diabetes enrolled in clinical trials. Nevertheless, some important insights into potential effects on renal function can be gained by examining estimated GFR (eGFR) measurements (creatinine based) obtained from these type 2 diabetes trials (65). Not surprisingly, based on effects in our patients with type 1 diabetes, SGLT2i in type 2 diabetes studies reduces eGFR after 3 to 4 weeks of therapy, suggesting a decline in intraglomerular pressure, similar to the effects expected with ACE inhibition (66,67). This effect is dose dependent and present in patients with a wide range of eGFR values, from 30 to 90 mL/min/1.73m², suggesting persistent effects even in patients with impaired renal function (67). Importantly, the effect of SGLT2 inhibition on eGFR is reversible after a 3-week washout period, reinforcing the concept that effects on GFR are hemodynamically mediated. Furthermore, these effects were durable throughout a 104-week treatment period (68). Interestingly, after the short-term decline at 4 weeks, eGFR remained stable during SGLT2 inhibition therapy as compared with a gradual decline during sulfonylurea treatment, despite similar glycemic control.

This pattern of an acute eGFR decrease followed by greater preservation of renal function over time is highly suggestive of a beneficial reduction in renal hyperfiltration resulting in renal protection, similar to the expected effects of RAAS inhibition (49,69). For example, in patients enrolled in the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan (RENAAL) trial, the greater the acute fall in eGFR with the angiotensin-II receptor blocker losartan, the slower the long-term rate of eGFR decline (70). Whether acute GFR declines with SGLT2 inhibition also translate into long-term renal protection is not yet known. Finally, although the individual effects of SGLT2 inhibition and ACE inhibition on renal function are known, the physiologic and clinical effects of combining these agents need to be clarified, as simultaneous blockade of neurohormonal and tubular factors may lead to synergistic protective effects.

**Conclusion**

Inhibition of SGLT2 may represent a promising new therapy for patients with type 1 diabetes, owing to its effects on metabolic parameters and renal function. Although outside the scope of this review, SGLT2 inhibition also has important clinical effects on lowering blood pressure in type 2 diabetes and type 1 diabetes (12). As described elsewhere (12), the mechanisms responsible for blood pressure lowering are likely mediated by several factors, including diuretic effects, improved arterial compliance, weight loss, improved glycemic control and anti-inflammatory pathways (Figure 3). Because early blood pressure abnormalities are common in type 1 diabetes, further benefits of SGLT2 inhibition for renal protection may be derived through improved blood pressure.
control. Based on promising experimental and human data, future long-term trials are clearly required to determine the clinical effects of SGLT2 inhibition on glycemic control, blood pressure and renal outcomes of patients with type 1 diabetes.

**Author Disclosures**

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