

# Role of sodium glucose cotransporter-2 inhibitors in type I diabetes mellitus

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**Abstract:** The burden of diabetes mellitus (DM) in general has been extensively increasing over the past few years. Selective sodium glucose cotransporter-2 (SGLT2) inhibitors were extensively studied in type 2 DM and found to have sustained urinary glucose loss, improvement of glycemic control, in addition to their proven metabolic effects on weight, blood pressure, and cardiovascular benefits. Type 1 DM (T1D) patients clearly depend on insulin therapy, which till today fails to achieve the optimal glycemic control and metabolic targets that are needed to prevent risk of complications. New therapies are obviously needed as an adjunct to insulin therapy in order to try to achieve optimal control in T1D. Many oral diabetic medications have been tried in T1D patients as an adjunct to insulin treatment and have shown conflicting results. Adjunctive use of SGLT2 inhibitors in addition to insulin therapies in T1D was found to have the potential to improve glycemic control along with decrease in the insulin doses, as has been shown in certain animal and short-term human studies. Furthermore, larger well-randomized studies are needed to better evaluate their efficacy and safety in patients with T1D. Euglycemic diabetic ketoacidosis incidences were found to be increased among users of SGLT2 inhibitors, although the incidence remains very low. Recent beneficial effects of ketone body production and this shift in fuel energetics have been suggested based on the findings of protective cardiovascular benefits associated with one of the SGLT2 inhibitors.

**Keywords:** glycemic control, glycosylated hemoglobin, euglycemic diabetic ketoacidosis, oral antidiabetics

## Introduction

Diabetes mellitus (DM) is a growing public health concern worldwide. The number of DM patients was estimated to be 382 million based on statistics in 2013, and this number is further expected to rise to 592 million by the year 2035.<sup>1</sup> DM is a chronic illness, characterized by high blood glucose level, resulting from impairments in insulin secretion, defects in insulin action, or both. DM is further classified into three main types: type 1 DM (T1D), type 2 DM (T2D), and gestational DM.

T1D occurs mainly due to autoimmune destruction of the insulin-producing pancreatic B-cells, leading to absolute insulin deficiency, where >80% of those cells are being destroyed.<sup>2,3</sup> Its incidence is increasing and it currently accounts for 5%–10% of all the cases of diabetes. More so, insulin therapy, the mainstay of therapy for T1D patients, proposes many challenges to physicians and patients.

Despite the clear beneficial advances over the past years in insulin formulation and its way of delivery in patients with T1D, continuous subcutaneous insulin infusion and continuous glucose monitoring (CGM) systems still fail to achieve the optimal

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metabolic targets that are needed to prevent risk of complications and are associated with weight gain and potential cardiovascular complications.<sup>4</sup>

Different oral antidiabetic drugs were tested in randomized controlled trials as adjunctive-to-insulin therapy. These include metformin,<sup>5,6</sup> thiazolidinediones,<sup>7,8</sup> alpha-glucosidase inhibitors,<sup>9,10</sup> and incretin therapies, which include amylin analogs,<sup>11,12</sup> dipeptidyl peptidase-4 (DPP-4) inhibitors,<sup>13</sup> and glucagon-like peptide-1 receptor agonists,<sup>14,15</sup> with no consistent results with regard to insulin dose adjustment or HbA1c level.<sup>5–15</sup>

It is clear that there remains considerable room for trying to improve outcomes of treatment of patients with T1D. Exploration of new therapies is obviously needed as an adjunct to insulin in order to try to achieve optimal metabolic control in T1D patients.

Sodium glucose cotransporter-2 (SGLT2) inhibitors have been studied in T1D in animal and human studies and may be useful to improve glycemic control, as adjunctive-to-insulin therapy. This review highlights briefly the history of SGLT2 inhibitors as well as their use in T2D, focusing on their promising potential in T1D.

## History of SGLT inhibitors

The history of SGLT2 inhibitors goes back to the late 1800s, when a compound called phlorizin, a natural phenolic O-glucoside, was found in the bark of apple trees and was put to use in multiple ways, most notably due to its physiological ability to cause glucosuria. Phlorizin was found to be a competitive nonselective inhibitor of both SGLT1 and SGLT2, had poor oral bioavailability, and was found to be toxic. This significantly limited its use later on. Moreover, clinical mutations of SGLT1 were found to be associated mainly with intestinal malabsorption of glucose and galactose and had little or no glucosuria effect. On the other hand, individuals with mutations in SGLT2 had no intestinal manifestations, but had persistent renal glucosuria, often in the range of 60–120 g/day.<sup>16</sup>

This led to extensive studies, which eventually led to the development of longer acting and more selective SGLT2 inhibitors, which were found to be effective antidiabetic agents and suitable for once-daily dosing without having harmful SGLT1 inhibiting effects. These medications were found to be effective as selective SGLT2 inhibitors, especially since diabetic patients have upregulation of the renal expression of SGLT2; therefore, the glucosuric and blood glucose lowering effect of SGLT2 inhibition was expected to be of great importance.<sup>17,18</sup>

## Efficacy of SGLT2 inhibitors in T2D

SGLT2 inhibitors are oral antidiabetic agents currently approved for treatment of T2D. The first agent among these selective agents was dapagliflozin, launched by AstraZeneca and Bristol–Myers Squibb Company, and approved in the European Union in late 2012.<sup>19</sup> This was later followed by canagliflozin, launched by Janssen Research and Development, and approved in 2013 by the US Food and Drug Administration (FDA).<sup>20</sup> Empagliflozin, which was launched by Boehringer Ingelheim Pharmaceuticals, was later approved in 2014 by the US FDA.<sup>21</sup>

All these SGLT2 inhibitors led to sustained urinary glucose loss of ~40–80 g/day and were found to be associated with good blood glucose lowering efficacy in T2D in addition to other beneficial effects such as lowering of body weight.<sup>17–19</sup>

SGLT2 inhibitors have clearly proven their efficacy in many different placebo-controlled trials in patients with T2D who were treated with diet and exercise,<sup>22,23</sup> as well as add-ons to other glucose-lowering agents, such as metformin,<sup>24–27</sup> sulfonylurea,<sup>28–31</sup> pioglitazone,<sup>32–34</sup> DPP-4 inhibitor,<sup>35,36</sup> in triple oral therapies and in combination with insulin.<sup>37</sup> They were found to be as active<sup>38–49</sup> or even superior to other glucose lowering agents (sulfonylureas or sitagliptin).<sup>29,36</sup> In a review article by Sheen, analysis of the various SGLT2 inhibitors randomized controlled trials demonstrated a very consistent effect on reduction in HbA1c and body weight, whatever the background glucose lowering therapy and the nature of the SGLT2 inhibitor used.<sup>40</sup>

Moreover, SGLT2 inhibitors are characterized by their added benefits to address unmet clinical needs, such as weight loss, lipid lowering, and blood pressure control.<sup>42,43</sup> They are generally well tolerated. The most prevalent adverse event associated with SGLT2 inhibitors consists of urinary and genital infections.<sup>6</sup> Reversible increases in serum creatinine, prerenal in origin or secondary to tubular glomerular feedback mechanisms, have been reported.<sup>43</sup> Low-density lipoprotein cholesterol concentrations also rise by ~5%, but are counterbalanced by increases in high-density lipoprotein cholesterol and reductions in triglyceride levels.<sup>40</sup> Increase in hemoglobin concentrations and also hematocrit and hypoglycemia have been reported when SGLT2 inhibitors are combined with sulfonylureas or with insulin.<sup>43</sup> Cases of euglycemic diabetic ketoacidosis (DKA) have been described, leading to issuing a US FDA warning in that matter.<sup>43</sup> SGLT2 inhibitors can also increase urinary calcium excretion and/or serum phosphate levels.<sup>43</sup> Finally, increase in fracture rates has been reported with canagliflozin.<sup>43</sup>

## Efficacy of SGLT2 inhibitors in T1D patients

As mentioned earlier, SGLT2 inhibitors are approved for T2D treatment, but there has been off-label use of these drugs in T1D patients despite the very low risk of euglycemic ketoacidosis cases reported. Some of these cases occurred in T1D patients, although the majority pertained to T2D.<sup>43</sup>

Adjunctive use of SGLT2 inhibitors in T1D was found to have potential to improve glycemic control, as has been shown in animal and short-term human studies (refer to Table 1 for a summary of human studies).<sup>46–50</sup>

An animal model study evaluated the effect of empagliflozin alone and in combination with insulin therapy on glucose control in animals with T1D and has suggested that this agent may be useful to improve glycemic control, as adjunct to insulin therapy, in animals with T1D.<sup>44</sup> This former study was able to show that empagliflozin, when combined with low-dose insulin, showed similar glucose lowering efficacy, compared with high-dose insulin treatment alone.

Another animal study evaluated the potential efficacy of empagliflozin on recovering insulin pathways and improving pancreatic  $\beta$ -cell mass in streptozotocin-induced T1D mice, and again showed a beneficial effect on preserving  $\beta$ -cell regeneration, thus leading to improvement in blood glucose homeostasis.<sup>41</sup> It was further hypothesized that this may actually be due to pancreatic  $\beta$ -cell protection from the toxic effect of high glucose and its induction of oxidative stress.<sup>45</sup>

A study on humans evaluated the efficacy and safety of empagliflozin, given at a dose of 25 mg daily to 40 patients with T1D, for a total of 8 weeks.<sup>42</sup> It concluded that empagliflozin did improve glycemic control and reduced hypoglycemic events, insulin doses, and weight in this patient population.<sup>46</sup>

The efficacy of remogliflozin in three different doses, 50, 150, and 500 mg, was studied on plasma glucose levels, after a 75 g oral glucose challenge, in 10 T1D patients, who were insulin pump users.<sup>47</sup> 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 remogliflozin, before the oral glucose tolerance test.<sup>47</sup> Compared with placebo, remogliflozin was associated with substantial improvements in the glucose profile over 10 h, although mean glucose profiles were not as optimal as with prandial insulin.<sup>47</sup>

Dapagliflozin was evaluated in 70 adults with T1D who had uncontrolled HbA1c at baseline, ranging between 7% and 10%, and who were receiving stable doses of insulin.<sup>44</sup> Four dapagliflozin doses (1, 2.5, 5, or 10 mg) were tried

and compared with placebo over a period of 2 weeks. Dapagliflozin had dose-related reductions in 24h glucose monitoring and in insulin dosing, in addition to improvement in the overall glycemic variability, an emerging predictor of cardiovascular complications nowadays. Canagliflozin was also assessed in 351 adults with uncontrolled T1D, with a baseline HbA1c range between 7.0% and 9.0%, as an add-on treatment to insulin in an 18-week, double-blinded study.<sup>48</sup> Canagliflozin in its 2 doses, 100 and 300 mg, was compared with placebo in these patients who were already on multiple daily insulin injections or continuous subcutaneous insulin infusion. The study demonstrated that more patients had HbA1c reduction of  $>0.4\%$  with canagliflozin 100 and 300 mg versus placebo at the end of the study (36.9% and 41.4% vs 14.5%, respectively;  $P<0.001$ ).<sup>49</sup> Canagliflozin did not lead to an increase in body weight or hypoglycemia rates.<sup>49</sup> However, an increased incidence of ketone-related adverse events was noted (5.1%, 9.4% vs 0%), with canagliflozin 100 and 300 mg when compared with placebo.<sup>49</sup>

Sotagliflozin, a dual SGLT1 and 2 inhibitor, was assessed as an additional therapy to insulin in 33 patients with T1D, over a period of 29 days in a randomized, double-blinded trial. There was a significant reduction in total daily bolus insulin dose by 32.0% in the sotagliflozin group compared with 6.4% in the placebo group, which was accompanied by a significant reduction in the mean daily glucose level assessed by CGM of 148.8 mg/dL in the sotagliflozin group compared with 170.3 mg/dL in the placebo group.<sup>46</sup> Body weight decreased significantly in the sotagliflozin group (1.7 kg), while the placebo group had 0.5 kg gain.<sup>50</sup>

Moreover, SGLT2 inhibitors in T1D may have renal protective effects as they tend to lower intra-glomerular pressure, and this has recently been demonstrated with empagliflozin in patients with T1D.<sup>47,51</sup>

Despite the above mentioned studies which pointed toward the beneficial effects of SGLT2 inhibitors on dose reduction and glucose control in addition to insulin therapy in T1D patients, larger randomized controlled trials are needed in order to better assess their efficacy.

## Mechanisms by which SGLT2 inhibitors therapy would provide clinical benefit as adjunct to insulin in T1D

Studies in mice and humans have consistently shown that chronic high glucose levels would increase B-cell apoptosis and cell death, consequently resulting in abnormally decreased insulin levels in both T1D and T2D. In T1D specifically, it is mostly cytokine-induced destruction of the

**Table 1** Summary of human studies on the use of SGLT2 inhibitors in T1D patients

| Reference of study and trial type   | Subjects  | Characteristics of patients   | Drug name  | Drug dose           | Results   |
|---|---|---|--|---------------------|---|
| Perkins et al <sup>46</sup><br>Open-label proof of concept trial                                    | 40 adults with T1D on insulin therapy                           | 50% males, mean age was 24.3±5.1 years, and had 17.1±7.1 years diabetes duration and BMI 24.5±3.2 kg/m <sup>2</sup> with an HbA1c of 8.0±0.9%   | Empagliflozin vs placebo as an adjunctive to insulin for a total period of 8 weeks   | 25 mg daily         | Improvement in glycemic control, insulin doses, and weight  |
| Mudaliar et al <sup>47</sup><br>Single-center, randomized, double-blinded, placebo-controlled trial | 10 adults with T1D managed with continuous subcutaneous insulin | Not available   | RE, placebo, prandial insulin, as an adjunctive to insulin. Each subject participated in 5 treatment periods separated by 5–35 days                  | 50, 150, and 500 mg | RE significantly reduced the rise in plasma glucose concentration after oral glucose. Similar adverse events in all groups  |
| Henry et al <sup>48</sup><br>Randomized, double-blinded, placebo-controlled pilot study             | 70 adults with T1D on stable doses of insulin (HbA1c 7%–10%)    | 61.5% males, mean age was 35.3±12.9 years, and had 16.2±9.7 years diabetes duration and BMI 25.3±3 kg/m <sup>2</sup> with an HbA1c of 8.75±0.92%  | Dapagliflozin or placebo as an adjunctive to stable doses of insulin for a period of 7 days  | 2.5, 5, or 10 mg    | Within the dapagliflozin groups, there was an observed increase in urinary glucose excretion and dose-related reductions in 24 h glucose, glycemic variability, and insulin dose  |
| Henry et al <sup>49</sup><br>A double-blind, phase 2, randomized study                              | 351 adults with T1D on insulin (HbA1c 7.0%–9.0%)                | 63% males, mean age was 42±11.9 years, and had 23.3±11 years diabetes duration and BMI 28±3.6 kg/m <sup>2</sup> with an HbA1c in mmol/mol of 63±6.6   | Canagliflozin or placebo as an adjunctive to multiple daily insulin injections or continuous subcutaneous insulin infusion over a period of 18 weeks | 100 or 300 mg       | More patients had both HbA1c reduction ≥0.4% and no increase in body weight with canagliflozin 100 and 300 mg vs placebo with similar incidence of hypoglycemia. Diabetic ketoacidosis was seen with canagliflozin 100 and 300 mg vs placebo (4.3%, 6.0%, 0%, respectively) |
| Sands et al <sup>50</sup><br>A randomized, multicenter, placebo-controlled, double-blind trial      | 33 patients with T1D on insulin therapy                         | 47% males in placebo group vs 50% in sotagliflozin group, mean age was 34 years for placebo vs 45.5 years for sotagliflozin group. Patients had mean diabetes duration of 18.5 years in placebo group and 16.8 years for sotagliflozin group. Mean BMI 26.2±3 kg/m <sup>2</sup> for placebo group and 27.1±3.1 kg/m <sup>2</sup> for sotagliflozin group. HbA1c in mmol/mol 62.8±5.6 for placebo group and 63.3±6 for sotagliflozin group | Sotagliflozin or placebo as an adjunctive to previous insulin delivery regimen for a period of 29 days   | 400 mg              | Sotagliflozin decreased total daily bolus insulin use, lowered mean daily glucose measured by continuous glucose monitoring, and patients had more time in the target glycemic range. Body weight also decreased (1.7 kg) with sotagliflozin treatment                      |

**Abbreviations:** T1D, type 1 diabetes mellitus; SGLT2, sodium glucose cotransporter-2; BMI, body mass index; RE, remogliflozin etabonate.

pancreatic B-cells.<sup>52</sup> This appreciation of the importance of pancreatic  $\beta$ -cells in the pathogenesis of both T1D and T2D has led researchers to try to find ways to improve glucose homeostasis by preserving the function of these important cell types.<sup>53</sup> Studies were able to show that SGLT2 inhibitors have the ability to lead to B-cell regeneration.

A study in diabetic mice models suggested that SGLT2 inhibition preserved islet mass, through decreased

glucose-induced B-cell toxicity, and improved pancreatic B-cell functioning, where the frequency of cell death was calculated and assessed, and was shown that it significantly decreased with the drug.<sup>54</sup> This was again confirmed in another study carried out in streptozotocin-induced T1D rats in an insulin-independent manner, where empagliflozin was shown to recover insulin pathways by improving pancreatic  $\beta$ -cell mass.<sup>55</sup>

Canagliflozin, 100 and 300 mg doses, in humans was also shown to be capable of causing improvements in B-cell function with a resulting increase in fasting insulin secretion.<sup>56</sup> This  $\beta$ -cell preservation was found to occur through an insulin-independent mechanism.

## Euglycemic DKA and SGLT2 inhibitors

Although adverse events of SGLT2 inhibitors in T1D patients are similar to those in T2D, the risk of euglycemic DKA, especially after the US FDA warning, is worth mentioning.<sup>57</sup> In fact, SGLT2 inhibitors are known to reduce the glucose available for energy utilization. Therefore, in the event of any extra demand for glucose, the SGLT2-inhibited body may not be able to maintain its homeostasis, leading to a ketogenic metabolic pathway.<sup>57</sup> The alteration of insulin to glucagon ratio also plays a role in the pathogenesis of euglycemic DKA.<sup>58</sup> The subsequent relative insulinopenia will manifest as ketonuria when challenged with stress, and high glucagon levels are associated with nausea, which may precipitate or worsen loss of appetite.<sup>58</sup>

This has led the US FDA to issue warnings about this increased risk of euglycemic DKA associated with SGLT2 inhibitors.<sup>59</sup> The US FDA warning occurred after the reporting, in the FDA Adverse Event Reporting System database, of 20 clinical cases of euglycemic DKA, necessitating hospitalization, among SGLT2 inhibitors users, from the period between March 2013 and June 2014. There is currently an ongoing review, initiated by European Medicines Agency, trying to evaluate the risk of euglycemic DKA among T2D patients, utilizing either dapagliflozin, canagliflozin or empagliflozin.<sup>60</sup>

It is worth mentioning that recent studies have suggested that this increase in ketone bodies is not always as deleterious as it may seem but may have some potential protective effects on the heart. This speculation was brought about after the noted beneficial cardiovascular effect found with SGLT2 inhibitors. As for the analysis of this beneficial cardiovascular effect, there have been many speculations, among which are diuretic and hemodynamic effects, due to the reduction in blood pressure and the decrease in extracellular volume.

A new interesting speculation has been introduced and this has suggested that this continued loss of urinary glucose and calories, that occurs with SGLT2 inhibitors, would lead to an accelerated starvation situation, with an increase in glucose reabsorption and endogenous glucose production, partly related to an increase in glucagon and a decrease in insulin levels, with an increased dependence on fat oxidation

at the expense of glucose oxidation, which would then lead to an increase in free fatty acids and ketone bodies production.

Ketone bodies may have had a protective effect on the heart especially when the heart consumes and extracts them more efficiently compared with glucose and fatty acids, and thus may lead to an increase in myocardial contractility/renal work efficiency after this shift in the fuel utilization away from lipids and glucose, toward ketone bodies.<sup>61,62</sup>

Thus, the renal and cardiovascular benefit may be due to the shift in myocardial and renal fuel metabolism, which is found to occur with a rapid onset and is sustained in duration, which would explain this early noted improvement in cardiac and renal outcomes in these patients.<sup>63,64</sup>

These small beneficial changes in energetics can translate into large differences in efficiency over weeks to months. Good benefits in the heart would translate into kidney benefits as well and vice versa.

Detailed physiologic and imaging studies need to be performed in order to better understand the mechanisms behind these cardiovascular and renal benefits.

## Conclusion

It is clear that there remains considerable room for trying to improve control and outcomes of T1D patients. New therapies are obviously needed, as complementary to insulin, with the aim of achieving optimal glycemic and metabolic control in patients with T1D. The beneficial effects of SGLT2 inhibitors on dose reduction and glucose control were assessed and tended to be consistently beneficial, but larger studies are needed to reach in-depth conclusions with regard to their use in patients with T1D especially given the concern of euglycemic DKA. Detailed physiologic and imaging studies need to be done in order to better understand the mechanisms behind these cardiovascular and renal benefits noted with SGLT2 inhibitors.

## Disclosure

The authors report no conflicts of interest in this work.

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