Role of Sodium Glucose Co-Transporter-2 Inhibitors in Pre-diabetes and Their Extra-glycemic Effects

REVIEW

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Abstract

The burden of diabetes mellitus and pre-diabetes has been extensively increasing over the past few years. Selective sodium-glucose co-transporters inhibitors were extensively studied in type 2 diabetes mellitus and were found to have sustained urinary glucose loss, improvement in glycemic control, in addition to their proven metabolic effects. Although they sound to be promising, there is still no clear data regarding their use in the prevention of diabetes, in pre-diabetic individuals, a subset of patients who are at increased risk of development of type II diabetes and its complications. Moreover, sodium-glucose co-transporters inhibitors were found to have multiple extra-glycemic beneficial effects, including weight loss, blood pressure reduction and beneficial effects on the kidneys. Therefore, their use in pre-diabetes is postulated to be beneficial on glucose and metabolic profile and larger studies need to be conducted in this subset of population.

Keywords

Diabetes Mellitus, Pre-Diabetes, Sodium-Glucose Co-Transporters, Oral Diabetic Medications, Weight Loss, Cardiovascular Events.

Introduction

Tight glucose homeostasis is adequately maintained in healthy individuals through the regulation of glucose production, reabsorption, and utilization. Therefore, despite extreme variations in glucose intake, relatively few people develop diabetes or hypoglycemia. Moreover, in healthy individuals about 180 grams of glucose is filtered daily by the renal glomeruli, and is then reabsorbed in the proximal convoluted tubules (PCT), through the help of the passive facilitated glucose transporters (GLUTs), and the active, sodium-glucose co-transporters

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Table 1. Comparison between SGLT1 versus SGLT2.

Characteristics	SGLT 1	SGLT 2
Location	Apical membrane of small intestine absorptive cells (Enterocytes); later part of PCT (Segment 3) SGLT1 can also be located in the brain, skeletal muscle, lungs, liver, and kidney.	Exclusively found in the apical membrane of renal convoluted proximal tubules (S1 and S2)
Capacity	Low capacity	High Capacity
Affinity	High affinity	Low Affinity
Contribution to glucose reabsorption	<10%	More than 90%
Disease state if mutation/ deficiency occurs	Potentially fatal neonatal condition of glucose galactose malabsorption	Familial renal glucosuria
Physical manifestations of disease states	Severe diarrhea as of few days of age	None
	PCT: Proximal Convoluted Tubule. SGLT: Sodium-glucose co-transporter.	

(SGLTs) which utilize the Na^+-electrochemical gradient provided by the $Na^+–K^+$ ATPase pump in order to transport glucose into cells against its concentration gradient [1].

There are six identified SGLTs described, two of which (SGLT1 and SGLT2) are considered to be the most important and are described in **Table 1** [2-5]. SGLTs transport glucose across the luminal membrane of the cells lining the small intestine and across the proximal tubules of the kidneys [4]. SGLT2 turned out to be the major one involved in the active transport of glucose against its concentration gradient [5]. SGLT1 is thought to remove most of the remaining luminal glucose in the later sections of the proximal tubule [4-5].

It is well known that diabetes mellitus (DM) is a growing public health concern worldwide. In 2013, the number of patients with type II diabetes mellitus (T2D) was estimated to be 382 million; and by year 2035 this number is expected to rise to 592 million [6]. In addition, a much larger segment of the world's population is diagnosed with pre-diabetes. Pre-diabetes is defined by a blood glucose concentration higher than normal, but not meeting the definition of diabetes per se. The World Health Organization (WHO) defined pre-diabetes as impaired fasting glucose concentration (IFG) ranging between 110 mg/dl and 126 mg/dl, and/or impaired glucose tolerance (IGT), where the plasma glucose concentration, 2 hours post a 75 g oral glucose load, ranges between 140 mg/dl and 199 mg/dl. The American Diabetes Association (ADA) uses the same WHO definition for the post-load threshold values for impaired glucose tolerance but a lower cut-off value for the impaired fasting glucose (100-125 mg/dl). Furthermore, as per ADA, a glycated hemoglobin (HbA1c) between 5.7 and 6.4%, can also be used for diagnosing pre-diabetes as well. It is important to note that the ADA and the WHO recognize that an HbA1c level ≥6.5% is indicative of diabetes [6-9].

Around 316 million people worldwide or around 6.9% of adults are estimated to have impaired glucose tolerance and by the year 2035, this is even projected to increase to around 471 million, which is around 8.0% of the total adult population [10]

This review highlights pre-diabetes associated risks and the available treatment options. We also touched on the established role of SGLT2 inhibitors in T2D, further focusing on their potential in reversing pre-diabetes as well as their emerging extraglycemic beneficial effects.

Health Risks Linked to Pre-diabetes

The first well-known risk is the progression to T2D. In a meta-analysis, which evaluated the progression to diabetes in these patients, the annual incidence rate of diabetes was found to be between 4%-6% for patients with IGT, 6-9% for isolated IFG and 15%-19% for both IGT and IFG [11]. Other major studies reported similar increased annual incidence rates of conversion from pre-diabetes to diabetes. Increased risk of chronic kidney disease and early nephropathy was also found to be highly associated with pre-diabetes [12-13]. This association remains unclear but it was hypothesized that it may be due to the increased incidence of diabetes in this group or to the toxic effect of the high glucose level itself [14]. Patients with pre-diabetes were also found to have a higher frequency of idiopathic polyneuropathy, painful sensory neuropathy [15-16] and small fiber neuropathy [17-18]. In addition, it was found that around 8 percent of pre-diabetic patients had evidence of diabetic retinopathy [19]. Patients who were diagnosed with pre-diabetes were also found to be at increased risk of developing macro-vascular diseases although the reason for this increased risk is still unclear [20-21]. Aside from the classic complications, studies revealed increased risk of Alzheimer's disease in diabetics, as it makes neurons more vulnerable to amyloid and tau toxicity, and it is now postulated that pre-diabetic patients run the same risk through impaired insulin signaling or resistance [22]. Therefore, it is clear that, it is extremely important not to ignore this subset of patients who are not frankly diabetic but are at increased risk of developing DM.

Current Treatment Options for Patients with Pre-diabetes

The beneficial effects of lifestyle interventions were confirmed in the two largest diabetes prevention studies, the United States Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS) [23-24]. In the DPP study, intensive lifestyle interventions (ILS) led to a 58% risk reduction of diabetes development after a 3-year follow-up [23]. The lifestyle modification in the Finnish DPS consisted of weight reduction more than 5 percent, total fat intake less than 30 percent of energy intake, saturated-fat intake less than 10 percent of energy intake, fiber intake greater than or equal to 15 g per 1000 kcal, and exercise greater than 4 hours per week [24]. This resulted in 9% DM in the intervention group versus 20% among the control group over 3 years [24]. Another study showed that for every 1 kg decrease in weight, the future risk of diabetes development was reduced by 16% [25].

Several anti-diabetic drugs groups have been studied in context of pre-diabetes. These include biguanides, thiazolidinediones, α-glucosidase inhibitors and incretin based therapies [23, 26-33]. The class of drugs mostly linked to decreased incidence of diabetes development in pre-diabetics, were thiazolenediones. In the double-blinded placebo controlled Diabetes Reduction Assessment with Ramipril and rosiglitazone, rosiglitazone was found to decrease the incidence risk of diabetes by 60% over a 3-year period despite being associated with significant side effects including weight gain and a slightly higher incidence of heart failure (0.5% versus 0.1%) and total cardiovascular events (2.9% versus 2.1%) [26]. The collective evidence of trials on the role of metformin in patients with IGT suggested a 45% risk reduction for development of T2D [29]. In a randomized, double-blinded trial of 1,780 Japanese subjects, Voglibose significantly lowered the risk of progression to T2D (hazard ratio: 0.595] and significantly achieved a normal OGTT compared to placebo (hazard ratio 1.539) [30].

Different clinical studies investigated as well the effect of incretin-based therapy in patients with pre-diabetes. A study with vildagliptin showed that it reduced postprandial glucose excursions and improved islet cell function. This was associated with a small but significant reduction in HbA1c levels

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(– 0.15%, from a baseline of 5.9%) [31]. Liraglutide was mainly studied in obese and overweight pre-diabetic patients and showed improvement in steady-state plasma glucose concentration [32] and fasting plasma glucose [33].

Efficacy of SGLT2 inhibitors For Patients with T2D and Pre-diabetes

SGLT2 inhibitors have clearly proven their efficacy in many different placebo-controlled trials in patients with T2D treated with diet and exercise [34-36], and as add-on to other glucose-lowering agents such as metformin [37-40], sulphonylurea [41], pioglitazone [42-43], dipeptidyl peptidase-4 (DPP-4) inhibitor [44], triple oral therapy [44-47], and in combination with insulin [48]. They were also found to be active; or even more active than other glucose lowering agents (such as sitagliptin) [49].

A review of placebo-controlled randomized clinical trials on SGLT2 inhibitors by Sheen AJ, has shown significant reductions in HbA1c and a significant lowering of fasting plasma glucose when they were administered as monotherapy or in addition to other glucose-lowering therapies including insulin [50]. Also, in head-to-head trials, SGLT2 inhibitors exerted similar glucose-lowering activity to metformin, sulphonylurea or sitagliptin and the risk of hypoglycaemia was much lower with SGLT2 inhibitors than with sulphonylureas and was similarly low as that reported with metformin, pioglitazone or sitagliptin [50]. Of great importance is that SGLT2 inhibitors were also found to offer added benefit by addressing unmet clinical needs, such as weight loss, lipid and blood pressure control [51-53].

Although SGLT2 inhibitors use sounds promising because of their unique mechanism of action, there is no clear data regarding their use in the prevention of diabetes in pre-diabetic individuals. However animal and human data showed promising effects on improvements in beta cell function. A study on rats reported improvements in beta cell function in those treated with phlorizin, a competitive non-

selective inhibitor of both SGLT1 and SGLT2 [54]. Improvements in model-based measures of beta cell function was also observed in mixed meal tolerance tests in subjects treated with empagliflozin [55] and canagliflozin within the first day of treatment and after 6-12 months [56]. In addition, non-statistically significant improvements were observed in the acute insulin response to glucose in subjects treated with dapagliflozin for 3 months, with a significant increase from baseline glucose disappearance rate observed with dapagliflozin [57]. One additional improvement in patients on SGLT2 inhibitors was the peripheral insulin sensitivity. In two hyperinsulinemic-euglycemic clamp studies, ranging from 2 weeks to 3 months, treatment with dapagliflozin was found to increase glucose disposal rate of around 15-20% relative to placebo [57-58]. Insulin sensitivity was again found to be improved in patients who were treated with empagliflozin and canagliflozin, assessed with the use of mixed-meal tolerance test–based measurements [55-56]

It is obvious that longer and larger studies are needed to assess whether SGLT2 inhibitors slow the progressive decline in b-cell function that occurs in pre-diabetes as they do in patients with diabetes and to translate the above physiologic mechanisms into palpable clinical benefits.

Extra Metabolic Effects of SGLT2 inhibitors

A. Protective effects of SGLT2 inhibition on the kidneys and cardiovascular system

Hyperglycemia was shown to increase the tubular glucose load, exposure, and reabsorption. Thus, preventing proximal tubule reabsorbtion of glucose through SGLT2 inhibitors may attenuate the detrimental effects of glucose on the diabetic kidney and eventually delay the development of diabetic nephropathy [59-60]. Studies on Akita mice showed that empagliflozin did not prevent but strongly attenuated kidney growth as was shown by reduced molecular markers and reduced inflammation in proportion to hyperglycemia [61]. In another rat mo-

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del study of T2DM, luseogliflozin prevented the fall in GFR and decreased the degree of glomerular injury, renal fibrosis, and tubular necrosis. In addition, in combination with the renin angiotensin system (RAS), SGLT2 inhibition had additive reno-protective effects compared to either drug alone [62].

Recent secondary outcomes results from the EMPA-REG OUTCOME trial on Empagliflozin in patients with T2D at high risk for cardiovascular events were published and revieled that those who received empagliflozin in addition to standard care [RAS inhibitors] had a significantly lower risk of microvascular outcome events than did those receiving placebo, a difference that was driven by a lower risk of progression of kidney disease [63]. In addition, patients in the empagliflozin group also had a significantly lower risk of progression to macroalbuminuria or clinically relevant renal outcomes, such as a doubling of the serum creatinine level and initiation of renal-replacement therapy [63]. The authors postulate that the following mechanisms explain the observed effects: reduction of proximal tubular sodium reabsorption, leading to increase distal sodium delivery to the macula densa thereby activating tubuloglomerular feedback and leading to afferent vasomodulation and a decrease in hyperfiltration, reduction in the intraglomerular pressure as well as other effects on arterial stiffness, vascular resistance, serum uric acid levels, and the systemic and renal neurohormonal systems [63].

All of the above mentioned results clearly indicate that SGLT2 inhibition can reduce diabetic kidney growth, inflammation, and injury despite the high glucose load downstream of the early proximal tubule.

B. Reduction in Blood Pressure

Due to the fact that SGLT2 inhibition induces a modest glucose-based osmotic diuresis and a small natriuretic effect, a reduction in systolic blood pressure [BP] of around 3-6 mm Hg was noted in patients with DM, which is considered to be comparable to that achieved with other established BP-lowering agents and therefore would be anticipated to have a vascular protective effect specially in high risk patients [64]. A recent review of SGLT2 inhibitors which looked at the blood pressure–lowering effects of dapagliflozin and canagliflozin, in both hypertensive and normotensive patients with T2D, demonstrated a 4-10 mmHg reduction in systolic blood pressure [65]. Moreover, a large study looked at the effectiveness and safety of empagliflozin on blood pressure reduction, using a 24-h ambulatory blood pressure monitoring, in 800 subjects with T2D whose mean age was 60 years and who had good kidney function but were either normotensive (<140/90 mmHg) or had stage 1 hypertension (blood pressure between 140/90 and 160/99 mmHg) [66]. Despite being a co-primary end point, there was a significant reduction in 24-h systolic and diastolic blood pressures; 4 and 2 mmHg respectively, lower than placebo at the high empagliflozin dose (25mg) [66]. The question arises about possible synergistic blood pressure lowering effects when SGLT2 inhibitors are added to other anti-hypertensive classes. In a double-blind, placebo-controlled, phase 3 study on patients with uncontrolled T2D and hypertension receiving a RAS blocker and an additional antihypertensive drug, Dapagliflozin blood pressure-lowering properties were particularly favourable in patients already receiving a beta blocker or calcium-channel blocker [67]. Also, in an investigation that studied patients with T1D treated with empagliflozin 25 mg daily for a period of 8 weeks, significant blood pressure reductions were noted in addition to a significant decrease in radial augmentation index, carotid augmentation index, and aortic augmentation index, with no significant changes in sympathetic nervous system activity measurements [68].

The exact mechanism of blood pressure lowering with these agents is not completely understood; however, is assumed to be related to its osmotic diuretic effect. They also have a very slight natriuretic effect, much less when compared to low-dose

thiazides. Weight loss may also be a contributing mechanism although the blood pressure effect is seen much earlier than the weight loss effect.

C. Weight Loss

Treatment with SGLT2 inhibitors was also found to offer weight loss benefits in overweight/obese patients with T2D [69]. In a meta-analysis of 12 randomized-controlled trials, dapagliflozin was found to cause a statistical significant 2.10 kg weight loss, while in another one, dapagliflozin treatment was also associated with a significant reduction in body weight of 1.63 kg [70-71]. It is primordial to differentiate between water and fat loss. Dapagliflozin was shown to cause a reduction in total body weight, predominantly by reducing fat mass, visceral adipose tissue and subcutaneous adipose tissue in T2D inadequately controlled with metformin, at 24 weeks [72]. These findings were again confirmed over a period of 102 weeks, where dapagliflozin was shown to improve glycemic control, and reduced weight and fat mass [73]. This weight loss effect was associated with improvement in overall health-related quality of life [74].

In a meta-analysis of ten trials, another SGLT 2 inhibitor, canagliflozin was found to cause greater body weight loss when compared to placebo (weight mean difference of 2.81 kg), especially with the 300 mg/day dose which was found to be superior in terms of weight loss reduction to 100 mg/ day in all trials [75]. In another trial, it was shown that canagliflozin-associated weight reduction also offers some advantages over sitagliptin, which was weight-neutral [76]. Also a phase II study evaluated the effects of canagliflozin on body weight in overweight and obese individuals without diabetes and it was shown that it significantly reduced body weight compared with placebo, with a least squares mean percent changes from baseline of 22.2%, 22.9%, 22.7%, and 21.3% with canagliflozin 50, 100, and 300 mg and placebo [77]. A slightly greater reduction in visceral adipose tissue than in subcutaneous adipose tissue was found upon analysis of abdominal fat in the canagliflozin groups with computed tomography imaging [78].

Just in accordance with other SGLT 2 inhibitors, empagliflozin was associated with modest but significant body weight loss (WMD -1.84 kg vs -1.38 kg in placebo), in a meta-analysis of ten randomized controlled trials but with no obvious weight loss difference between 10 and 25 mg in the various trials [79]. Empagliflozin-associated weight loss contrasted with the weight gain induced by a sulphonylurea [80] and the weight neutrality observed with sitagliptin [81]. There are no available data on body composition with empagliflozin.

Conclusion

The role of SGLT-2 inhibitors in pre-diabetic patients should definitely be better assessed and evaluated as data has been very promising in patients with T2D and the potential benefits are backed up by plausible physiologic mechanisms.

Moreover SGLT 2 inhibitors were found to have multiple extra-glycemic effects, including weight loss, blood pressure reduction and possibly beneficial effect on the kidneys and prevention of the dreaded microvacular complications.

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