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SODIUM GLUCOSE COTRANSPORTER 2 (SGLT2), A NEW APPROACH IN TYPE 2 DIABETES MELLITUS TREATMENT

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ABSTRACT

Although antidiabetic agents have been developed to target one or more of the core defects of type 2 diabetes mellitus (T2DM), many patients do not achieve glycemic goals. Inhibition of the sodium-glucose cotransporter 2 (SGLT2) induces glycosuria, reduces glucose toxicity and improves insulin sensitivity and β-cell function. As the mechanism of action of SGLT2 inhibitors is different from other agents and completely insulin-independent, the use of these drugs might potentially be efficacious alone or in combination with any other antidiabetic drug, including insulin. SGLT2 inhibitor approved for use in adult patients with T2DM as monotherapy in patients intolerant of metformin or as adjunctive therapy in patients inadequately controlled on existing antidiabetic medications, including insulin. A literature search conducted using PubMed identified key publications related to the use of SGLT2 in the treatment of patients with diabetes mellitus. No date limits were applied. Clinical trials published to date show that SGLT2 is safe and effective as monotherapy or as an add-on to insulin or oral antidiabetic agents in patients with T2DM.

KEYWORDS: Antidiabetic drugs, Glycosylated hemoglobin, Glycemic control, Sodium-glucose cotransporter 2 inhibitors, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Weight reduction.

INTRODUCTION

The pathophysiology of type 2 diabetes mellitus (T2DM) is complex and multifaceted. The core defects of T2DM include quantitative and qualitative β-cell dysfunction, peripheral (skeletal muscle) insulin resistance, and elevated glucose production in the liver, as well as increased lipolysis when obesity is present. However, it is becoming accepted that other known mechanisms, including increased glucagon, decreased incretin effect, increased glucose reabsorption in the kidneys and some neurotransmitter dysfunction, are also involved in the pathophysiology of T2DM.[1] The currently available antidiabetic agents have been developed to target one or more of the underlying defects or processes involved in T2DM.[2] Generally, glycemic control in patients with T2DM is poor, with only approximately 53 % of patients achieving glycemic goals with their current treatment regimen.[3] However, even in patients with good glycemic control, the progressive nature of T2DM means that most patients will eventually require multiple antidiabetic medications to manage their disease.[4] Metformin is the standard and preferred first line pharmacological drug for type 2 diabetes.[5] After metformin failure; various drugs are available as add-on therapy, such as sulphonylureas, insulin, thiazo lidinediones, and incretins. However, many of these drugs not only reduce glucose concen trations, but also cause weight gain and increase the risk of hypoglycaemia.[5] Thus, drugs are needed that can provide glycaemic control while having beneficial effects on weight and hypoglycaemia. This review discusses one of the most recently discovered classes of antidiabetic agents, the inhibitors of the sodium-glucose cotransporter 2 (SGLT2). SGLT2 inhibitors currently approved or under investigation include dapagliflozin, canagliflozin, empagliflozin and ipragliflozin; this manuscript will focus on the efficacy and safety of the highly selective and reversible SGLT2 inhibitor dapagliflozin, primarily in patients with T2DM.

Sodium Glucose Cotransporter 2 Inhibitors

Renal tubule regulation of glucose reabsorption by the kidney in the non-diabetic individual is shown in Fig. 1. Inhibition of SGLT2 results in a lowering of the threshold for renal glucose excretion and an increase in urinary glucose excretion, with an associated reduction in plasma glucose levels and the potential to decrease glucose toxicity with chronic administration.[6,7,8] The action of SGLT2 inhibitors is glucose-dependent, becoming negligible when plasma glucose concentration drops below 90/mg/dL, so the risk of hypoglycemia is lower than with insulin-dependent antidiabetic drugs.[9]

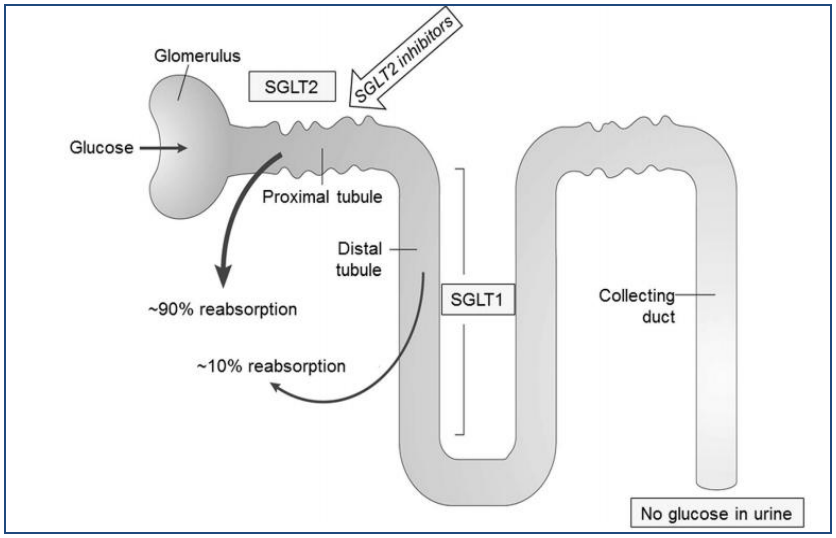

Figure. 1: Glucose reabsorption by the normal kidney, showing the site of action of sodium-glucose cotransporter (sglt2) inhibitors.[6]

Evidence suggests that glycosuria induced by SGLT2 inhibitors can also significantly improve β cell insulin secretion and insulin sensitivity in peripheral tissues, associated with a reduction in plasma glucose concentration[8,10,11,12,13] In addition, SGLT2 inhibitors as a class offer the clinical benefits of promoting body weight loss and produce a modest reduction in both systolic and diastolic blood pressure.[8,9,12,14-20]

The mechanisms of action of the blood pressure lowering effects of SGLT2 inhibitors are not fully understood. However, they are likely due to a mild osmotic diuretic effect in association with reductions in body weight and increased hematocrit, although it is possible that there may be a contribution from local inhibition of the rennin angiotensin system secondary to enhancement of sodium delivery to the juxtaglomerular apparatus.[14,17,21] Orthostatic hypotension is not increased with SGLT2 inhibitors.

Weight loss associated with SGLT2 inhibitors is biphasic, with an initial reduction in total body weight which can be attributed to fluid loss and a subsequent gradual continuous reduction resulting from increased urinary glucose excretion with associated loss of calories.[8,9,11,16]

The effects of SGLT2 inhibitors on hyperglycemia, body weight, and blood pressure suggest a favorable effect on cardiovascular risk factors. However, data on long-term effects on major cardiovascular outcomes, including myocardial infarction, stroke, and other vascular endpoints, are for the most part still under investigation, with results expected over the next

few years[12,16,20] Results of studies available to date show that empagliflozin ameliorated cardiovascular injury, coronary artery remodeling, and vascular dysfunction in a T2DM model in obese mice, suggesting a possible role in preventing diabetic macro vascular and micro vascular complications[22], and did not prolong the QT interval in healthy volunteers.[23] Empagliflozin was also associated with a decline in arterial stiffness, a marker for renal and cardiovascular clinical outcomes, in young patients with type 1 diabetes mellitus (T1DM).[15] SGLT2 inhibitors as a class have generally been shown to be as effective as other antidiabetic agents, with a good safety profile.[9,24] Data from phase II/III clinical trials, pooled analyses of randomized controlled trials, and systematic reviews show that SGLT2 inhibitors are as effective as other antidiabetic agents such as metformin, sulfonylureas, or dipeptidyl peptidase-4 (DPP-4) inhibitors in head-to-head trials, and may offer better long term glucose-lowering efficacy.[8,9,12,18,24,25]

The risk of hypoglycemia is lower with SGLT2 inhibitors than with conventional antidiabetic agents, but there is a higher risk of genital infections (mostly mycoses on the external genitals).[8,9,12,16,18,20,24] The effects of SGLT2 inhibitors on macrovascular and micro vascular outcomes are yet to be determined in human studies; however, adding SGLT2 inhibitors, and specifically dapagliflozin, to the standard of care was recently projected to reduce cardiovascular and micro vascular complications associated with T2DM, in a human model study using simulation methodology.[26]

The efficacy of SGLT2 inhibitors is influenced by the level of hyperglycemia and renal function.[9,16,21] Patients with substantial levels of hyperglycemia have a greater level of urinary glucose excretion and plasma glucose reduction. Conversely, patients with a lower glomerular filtration rate have a lower level of urinary glucose excretion, which is likely to lead to a lesser glucose-lowering effect.[27] Long-term study of patients with T2DM and moderate renal impairment showed that, although dapagliflozin reduced weight and blood pressure, glycemic control was not improved.

Effects on Hemodynamics

The favorable effects of SGLT2 inhibitors on a number of conventional CV risk factors, such as BP, blood glucose levels and body weight, are well documented (Fig. 2). Clinical studies are under way to investigate other effects of these drugs on other CV risk factors and outcomes.[28]

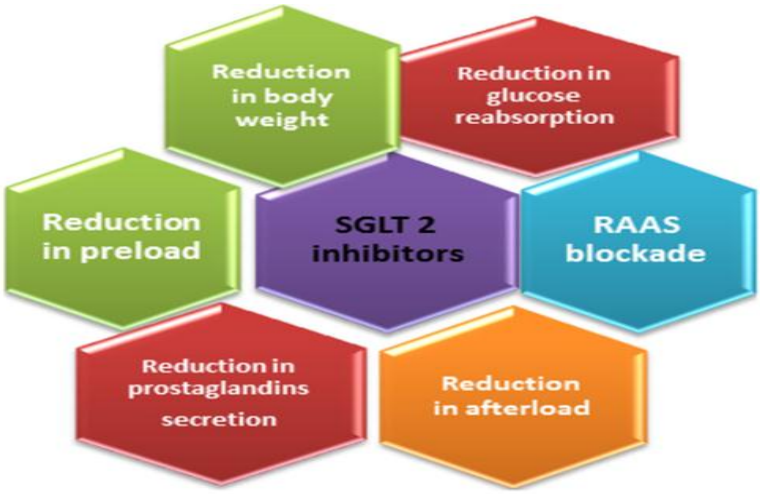

Figure. 2: Various Pharmacological actions of SGLT2 inhibitors. RAAS rennin aldosterone angiotensin system, SGLT2 sodium-glucose cotransporter 2.[28]

In particular, the osmotic diuresis effects of SGLT2 inhibitors have received considerable attention. Along with blocking glucose reabsorption, SGLT2 inhibitors also reduce protein and sodium reabsorption in the nephron, resulting in a mild osmotic diuresis.[29] The loss of volume and sodium activates the renin-angiotensin-aldosterone (RAAS) system and initiates a counter regulatory compensatory mechanism by the kidneys to maintain sodium homeostasis[30] (Fig. 2). In addition, weight loss resulting from glycosuria and the associated net caloric loss may further contribute to BP lowering.

Preload Reduction

Because of their intriguing effects on renal hemodynamics, it has been suggested that SGLT2 inhibitors could have a role in treating T2DM patients with both types of chronic heart failure (HF), namely reduced ejection fraction HF (HFrEF) or preserved ejection fraction HF (HFpEF). HFrEF is characterized by a left ventricular ejection fraction of B50%, increased left ventricular mass, as well as increased end-diastolic and end-systolic volume. This is typically seen in diabetic cardiomyopathy, valval heart diseases and cardiomyopathy. In contrast, HFpEF is characterized by a left ventricular ejection fraction of [50%, increased left ventricular mass, unchanged or decreased end-diastolic and end-systolic volume. This type of HF is seen in restrictive cardiomyopathy, hypertensive heart disease, and hypertrophic obstructive cardiomyopathy. SGLT2 inhibitor-induced diuresis would be expected to result in preload reduction (Fig. 2), which may be beneficial in chronic HF patients with a reduced ejection fraction. However, care should be taken when using diuretics in such patients, due to the possibility of excessive preload reduction.[31]

Afterload Reduction: There is evidence that SGLT2 inhibitors may reduce afterload as well as preload. Cherney et al. studied hemodynamic changes in type 1 diabetes mellitus patients who were treated with empagliflozin 25 mg daily for 8 weeks. This study documented reductions in BP, arterial stiffness and sympathetic nervous system activity. Radial artery and carotid waveforms, augmentation index (AIx), heart rate, and aortic pulse wave velocity were measured. The AIx is an indicator of central aortic pressure enhancement by a reflected pulse wave and is used as a predictor of adverse CV events. AIx is a ratio calculated using BP waveforms; the greater the augmentation or enhancement, the greater the degree of arterial stiffness. After 8 weeks of treatment, AIx was significantly reduced in the empagliflozin group, compared with the placebo group, suggesting reductions in the afterload as well as the preload (Fig. 2). No significant changes in sympathetic nervous system activity were reported[32], further suggesting that SGLT2 inhibitors reduce afterload. SGLT2 inhibitors have also been reported to reduce the levels of plasma uric acid. This is thought to be due to their effects on a urate transporter, solute carrier family 2, facilitated glucose transporter member 9, which transports urate into the urine in exchange for glucose.[33]

Effects on BP: Almost all SGLT2 inhibitor studies have reported significant BP reductions, with a larger effect on SBP (1.66–6.90 mmHg) than on DBP (0.88–6.99 mmHg) (Fig. 2). A pooled analysis of 4 Phase III, placebo-controlled clinical studies indicated modest reductions in SBP with canagliflozin (-3.3 and -4.5 mmHg with the 100 and 300 mg doses, respectively)[34]. Similarly, analysis of pooled data from 4 Phase III empagliflozin clinical trials revealed significant placebo-adjusted reductions in SBP with empagliflozin treatment (10 or 25 mg once daily for 24 weeks as a monotherapy or add-on therapy to metformin, metformin plus sulfonylurea, or pioglitazone with or without metformin)[35]. There are reports that dapagliflozin had effects on reducing the BP. In a study, which compared dapagliflozin as monotherapy in various dosing schedule vs. placebo in T2DM patients, reported reduction in office SBP and DBP in those patients up to -5.7 and 3.3 mmHg, respectively. Few studies had explored the efficacy of this drug as an add-on to the oral antidiabetics. In a study consisting of over 800 patients with T2DM who were on stable insulin dose with or without other oral antidiabetics, on add on dapagliflozin or placebo, the researchers reported reductions in SBP with dapagliflozin (mean change: -1.49 mmHg in the placebo group vs -5.30, -4.33, and -4.09 mmHg in the groups receiving 2.5, 5, and 10 mg of dapagliflozin, respectively) and non-significant DBP reductions (-1.31 with placebo vs. -2.96, -2.64, and -2.85 mmHg in the groups who received 2.5, 5, and 10 mg of dapagliflozin).

Effect on Pulse: There is no increase in pulse rate with SGLT2 inhibitors. A 104-week outcome study of canagliflozin indicated that the 100 and 300 mg dose reduced SBP and DBP compared with glimepiride, with no notable changes in pulse rate.[36] This contrasts with the tachycardic reported with use of other glucose lowering drugs such as glucagon like peptide 1 receptor agonists. In the short term, these BP-lowering effects have been attributed to both preload and afterload reduction. This is a unique feature of SGLT2 inhibitors, which needs to be highlighted in cardiology circles. Long-term effects may be mediated through RAAS activation and/or reductions in body weight.[30]

Effects on Body Weight: Reductions in body weight are consistently observed with SGLT2 inhibitor treatment (Fig. 2). This effect may be attributed to diuresis or volume depletion, as well as to net loss of calories in the form of glucose. Among T2DM patients inadequately controlled with metformin, weight loss occurred with dapagliflozin treatment, compared with weight gain on glipizide (-3.2 vs. ?1.4 kg over 52 weeks of treatment, dapagliflozin vs. glipizide; P\0.0001)[36]. Similar observations have been made regarding canagliflozin treatment. In T2DM patients inadequately controlled with metformin and sulfonylureas, reductions of -1.9 and -2.5 kg were achieved with 100 and 300 mg canagliflozin, vs. -0.8 kg with placebo.[35,37] Weight loss with SGLT2 inhibitors was also documented in patients who were taking a combination of oral antidiabetic drugs and insulin (P\0.001). The sustained impact on body weight is thought to be the result of fat loss.

CONCLUSIONS

The SGLT2 inhibitors are a new class of antidiabetic agents with a unique, insulin-independent mechanism of action that depends only on plasma glucose and renal function. SGLT2 inhibitors offer benefits beyond glycemic control, including modest reductions in body weight and blood pressure and improved insulin sensitivity and β-cell function.

The safety and efficacy of SGLT2 inhibitors (including canagliflozin, dapagliflozin and empagliflozin) for the treatment of hyperglycemia in T2DM has been well documented. For now, these drugs have proven to be a useful addition to the diabetes treatment arsenal, given their beneficial effects on CV risk factors. Looking to the future, the results of planned and ongoing trials to investigate long-term safety and efficacy of SGLT2 inhibitors, especially in terms of CV outcomes, will be of enormous interest. These results may provide additional motivation for investigating the use of SGLT2 inhibitors in the treatment of a broader range of CV-related conditions.

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