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Review Article

Safety and efficacy of sodium-glucose co-transporter 2 inhibitors in comparison with other Anti-diabetic agents: a scoping review

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Abstract

This review evaluates the safety and efficacy of SGLT2 inhibitors in relative to other conventional anti-diabetic agents. SGLT2 inhibitors are a new class of anti-diabetic medication that acts on the kidney and increase the urinary glucose excretion by inhibiting sodium-glucose cotransporter 2 in the proximal tubule. They have been evaluated in type 2 diabetes mellitus patients treated with diet/exercise, dual or combination therapy or insulin. Literature search was carried out in various electronic databases such as Google Scholar, trip database, Biomed center (BMC), Science Direct, JAMA, PubMed by considering inclusion criteria such as type 2 diabetes mellitus, adults, research articles, adjunctive therapy, gender (both), complications. SGLT2 inhibitors have some benefits beyond glucose control in relation to body weight, blood pressure, reduced cardiovascular events. Most reported adverse events are genital mycotic infections, urinary tract infections and events related to volume depletion.

Keywords: SGLT2 inhibitors; Anti-diabetic; Diabetes mellitus; Glucose excretion.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period [1]. It is a progressive disease, which requires combination therapy to maintain glycaemic control over time [2]. In type 2 diabetes mellitus (T2DM) there is an insulin resistance and a progressive loss of β-cell function which regulate the glucose throughout the body [3]. T2DM is associated with obesity, physical inactivity, increased blood pressure, abnormal blood lipid levels, and increased risk of thrombosis [4]. The majority of the increased mortality risk associated with type 2 diabetes is a result of cardiovascular disease (CVD). This demonstrates the importance of not only treating hyperglycemia but also managing the other contributory risk factors, including hypertension and dyslipidemia [5].

Along with diabetes, patients also face some microvascular and macrovascular complications, which is of a major concern and is also associated with high mortality rate [6]. T2DM, can lead to several serious and sometimes life-threatening complications are characterized by hyperperfusion of microvessels such as those in the eye and kidney, vascular remodeling, and arterial stiffening [7,8]. Most of the pharmacological agents currently used for treating hyperglycemia work by increasing either insulin activity or insulin secretion, and fall into one of four classes- Insulin sensitizers: e.g. metformin, thiazolidinediones, Insulin secretagogues: e.g. sulphonylureas (SU), glinides, DPP4 inhibitors, and, GLP 1 receptor agonists, Insulin (exogenous) and insulin analogs, Modulators of carbohydrate absorption/metabolism:e.g-alpha-glucosidase inhibitors [9].

Metformin is the standard first-line pharmacotherapy for the treatment of T2DM, unless it is contraindicated or not tolerated. Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as sitagliptin, are commonly used as second-line therapy and exert their Antihyperglycaemic effect by increasing concentrations of incretin hormones thereby enhancing insulin secretion. While the combination of metformin and sitagliptin has been shown to provide good glycaemic efficacy, as the disease progresses and glycaemic control declines, some patients may benefit from the addition of a third agent with a complementary mode of action [10]. There are

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labeled restrictions on the use of thiazolidinediones, metformin, sulfonylureas, and, more recently, glucagon-like peptide-1 (GLP-1) agonists [11,13]. Moreover, AHAs commonly used in this population, such as sulfonylureas, have been associated with an increased risk of hypoglycemia and weight gain [10-13]. Thus, new treatment options are needed for this growing population of patients with co-existing T2DM and renal insufficiency [14].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent the latest class of agents approved for the treatment of T2DM [15,16].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of AHAs in development that has a mechanism of action different from those of current therapies, with a primary effect on renal glucose handling. Specifically, induction of urinary glucose excretion (UGE) via inhibition of renal glucose reabsorption by SGLT2 provides an insulin-independent mechanism for lowering blood glucose and improving glycaemic control [17]. Normally, almost all filtered glucose is reabsorbed until the filtered load exceeds the glucose resorptive capacity. The plasma glucose concentration at which renal resorptive capacity is exceeded and UGE occurs is called the renal threshold for glucose (RTG). Renal glucose resorptive capacity is increased in T2DM, contributing to the worsening of hyperglycemia [18].

The most recent position statement [19] from the American Diabetes Association and European Association for the Study of Diabetes and the 2015 guidelines [20] from the American Association of Clinical Endocrinologists both address the use of SGLT2 inhibitors as an adjunct to diet and exercise to improve glycemic control in T2DM. This article summarizes current knowledge and practical considerations for the use of SGLT2 inhibitors.

Benefit analysis

Hyperglycemia

SGLT2 inhibitors showed major role regarding the reduction in glycated hemoglobin(HbA1c) when compared with from baseline analysis of RCTs, both as monotherapy and as add-on therapy of other glucose-lowering agents.

Canagliflozin

Patients initiated on CANA or DPP-4 agents, in which the patients initiated with CANA were more likely to have HbA1c measurements of <7% or 8% during the observation period compared to patients initiated on a DPP-4 agent [21]. In particular, with Grabner et al., [22] found that patients initiated on CANA were compared to patients initiated with sitagliptin who suffered more serious effects like neuropathy, obesity and had higher levels of HbA1c during their initial therapy.SGLT2 inhibitors lower glucose starting on the first day of initiation when compared with DPP-4 agents [23]. In accordance with Thayer et al., [24] identified that among CANA and DPP-4 inhibitor cohorts of 2,776 patients there is a change in HbA1c was greater among patients with CANA cohort than those with DPP-4 inhibitor cohort (−0.92% vs. −0.63%, $P < 0.001$), and greater percentages of the CANA cohort relative to the DPP-4 inhibitor cohort achieved HbA1c < 7% (35.4% vs. 29.9%, $P = 0.022$) over a 9 month follow-up.

Some findings shows that [25-28] the patients treated with canagliflozin has showed significant decrease in HbA1c from baseline values both as monotherapy (-0.77% and -1.03% at 26 weeks with canagliflozin 100 and 300 mg respectively;-0.73 % and -0.88 % at 52 weeks with canagliflozin 100 and 300 mg respectively) and as add-on therapy with other AHAs (-0.65 % and -0.74 % at 104 weeks on metformin with canagliflozin 100 and 300 mg respectively).

Greg Fulcher et al., [29] told that when canagliflozin compared with sulfonylureas there is a decrease of HbA1c of -0.74% and -0.83% for canagliflozin 100 and 330 mg respectively for 18 weeks and few studies supported his findings. According to American Diabetes Association (2012) Standards [30] and Inzucchi SE et al., [31] canagliflozin improved glycemic control when compared with placebo over 26 weeks and with sitagliptin over 52 weeks and inadequately controlled with metformin monotherapy.

Dapagliflozin

In a study by Christian Ott et al.,[32] slight decrease in HbA1c levels was observed with dapagliflozin when compared to placebo. The treatment period was found to be 6 weeks. The author or study reported significantly low

FPG and PPG levels after 6 weeks of dapagliflozin treatment. Insulin resistance was also lower with dapagliflozin than placebo during this six weeks period of treatment. Dapagliflozin may also have contributed to preventing arteriole wall thickening. In a study by Sonesson et al.,[33] there is a reduced hyperglycemia independently of insulin secretion or action and no increased risk of MACE in patients treated with dapagliflozin. Vasilakou D et al. [34] conducted analysis in 17,180 patients from 25 studies (14 dapagliflozin, one empagliflozin, and 10 canagliflozin studies) this analysis found no evidence for increased CV risk, with an SGLT2 inhibitor.

Ertugliflozin

In a study by Terra SG et al., there is a significant improvement in glycemic control with ertugliflozin compared to metformin and sitagliptin over 52 weeks of treatment. Ertugliflozin showed greater reductions in HbA1c compared with placebo from all baseline HbA1c subgroups. According to American diabetes association guidelines patients with ertugliflozin groups met the recommended HbA1c target of <7.0% (53 mmol/mol) 2 compared with the placebo group at Week 26. Ertugliflozin monotherapy improves HOMA-β, a marker of β-cell function **[**35]. In this study, improvements were also observed despite patients already receiving sitagliptin, which is known to improve β-cell function [36]**.** This is likely to be an indirect effect of reduced glucotoxicity resulting from enhanced urinary elimination of Glucose.

Ipragliflozin

In this study V.A. Fonseca et al., ipragliflozin showed a dose-dependent decrease of HbA1c over the 12-week study period compared with placebo. These results are similar to those from a dose-finding study with dapagliflozin by List et al. (2009). The Statistical difference between ipragliflozin and placebo groups of patient achieving HbA1c of 7.0% dose groups. The data showed that dosages of ≥50 mg compared to compare to metformin (1500 mg) showed lowering HbA1c and FPG in the 12-week study [37]**.**

Luseogliflozin

According to M Haneda et al., [38] over a 52-week treatment luseogliflozin decreased HbA1c as well as it is well of the lust of luseogliflozin bites with moderate renal impairment. In this study, the author evaluated safety and efficacy on renal function in 1000 Japanese patients with normal to moderately impaired renal function, HbA1c, FPG, and body weight decreased significantly from baseline to Week 52 in all groups, regardless of renal function. The change in HbA1c at Week 52 was 0.62% in patients having a moderate renal impairment with baseline HbA1c ≥8% to<9% and 1.27% in those with baseline HbA1c ≥9%, compared with 0.32% in patients (7.71% at baseline). By these results, we can suggest that luseogliflozin act as a therapeutic option for patients with moderate renal impairment whose baseline HbA1c is relatively high and who is at low risk of developing AEs**.**

Obesity/overweight

SGLT2 inhibitors play another role in obesity or overweight [39,40] Due to the caloric loss associated with increased UGE, treatment with SGLT2 inhibitors promotes weight loss to overweight/obese patients with T2DM [41]. In according to American diabetes association and Inzucchi SE et al., [30,31] treatment with canagliflozin has improved glycemic control and reduced body weight compared with placebo over 26 weeks and with sitagliptin over 52 weeks and it has shown better results in patients whose diabetes was inadequately controlled with metformin monotherapy**.** In a study by Greg Fulcher et al., [29] there is a significant decrease in body weight is seen with 300mg dose (-1.8) although not with the 100mg dose. But in some phase 3 studies have shown that there is a significant weight loss with the 100mg dose. According to Wilding JP et al.,[42] observed that there is significant weight loss comparing the canagliflozin 100 mg versus placebo in 26 weeks as add-on to metformin plus sulfonylureas**.** According to Yale et al., [43] canagliflozin 100 and 300 mg significantly reduced bodyweight when it compared with placebo after 26 weeks of treatment in subjects with T2DM and stage 3 CKD (eGFR ≥ 30 and <50 ml/min/1.73 m2). Ertugliflozin also showed beneficial effects on body weight [44,45]. In a study by V.A. Fonseca et al., 37 observed that there is a significant decrease in the body weight with 150 and 300

mg ipragliflozin treatment groups, resulted in a 5% weight loss among ipragliflozin treatment groups compared with placebo. With dapagliflozin, it has been shown that body weight loss in patients with T2DM inadequately controlled with metformin is predominantly explained by reduced total body fat mass, visceral adipose tissue, and subcutaneous adipose tissue volume (Bolinder et al., 2012).

According to Haneda et al., [38] after initiation of luseogliflozin significant decreased body weight from baseline to Week 52 in all groups, regardless of renal function. In Between-group comparisons, there are a smaller decrease in body weight in patients with moderate renal impairment (eGFR≥30 and <60 ml/min/1.73 m2) than in those with normal renal function (eGFR ≥90 mL/min/1.73m^2).

Blood pressure

SGLT2 inhibitors also provide a greater reduction in blood pressure, although the mechanism of BP reduction is incompletely elucidated [46]**.** In a study by Weir MR et al., **[**21] the patient initiated on CANA had significantly achieved a reduction of systolic blood pressure 140 mmHg compared with patients initiated on a DPP-4 agent. According to Ott et al., [8] after initiation of dapagliflozin therapy it lowered central SBP, resulting in a decreased PP (pulse pressure). While after treating with placebo central DBP was changed but there is no change in the central SBP so, resulting in a small increase in PP but not significant. These data indicate that dapagliflozin treatment caused a slight decrease in the stiffness of the aorta and its most proximal Branches.

Duvnjak et al., [47] found that the two DPP-4 inhibitors, sitagliptin, and vildagliptin, caused gradual decreases in AIx(augmentation index)and central SBP in patients with type 2 diabetes over 12 weeks of treatment, while Ott et al.,[8] demonstrated that lowered central SBP after 6 weeks of treatment with saxagliptin. Chilton et al.,[48] performed a post hoc analysis gathered data from a number of trials involving patients with type 2 diabetes, and found that empagliflozin significantly reduced PP and mean arterial pressure compared to placebo.

Lipids

The effect of SGLT2 inhibitors on lipid profile is rather limited and probably not clinically relevant **[**49]. Canagliflozin was associated with an average 8 % increase in plasma levels of low-density lipoprotein (LDL) cholesterol compared with placebo [50]. However, the potentially negative the effect is most probably compensated for by other beneficial lipid effects, such as increased high-density lipoprotein or HDL cholesterol and decreased triglycerides) [51]. Zinman B et al., [52] in EMPA REG OUTCOME, among T2DM patients with CVD mostly treated by lipid-lowering agents (statins), LDL cholesterol levels were slightly higher with empagliflozin than with placebo, but this adverse effect was compensated for by a concomitant increase in HDL cholesterol. According to Briand F et al. [53] observations showed that empagliflozin, via switching metabolism toward lipid utilization, moderately increases LDL cholesterol levels through reduced LDL catabolism.

Risk assessment

Urinary and genital infection

According to Geerlings et al., [54] it is shown that pharmacologically induced glucosuria with SGLT2 inhibitors, increases the risk of developing genital infections and, to a relatively lesser extent, urinary tract infections (UTIs). However, a definitive dose relationship of the incidence of these infections with the SGLT2 inhibitor doses or with the amount of UGE was not evident in the existing data**.** SGLT2 inhibitors were significantly associated with an increased risk of genital infections by 35% and urinary tract infections by 29%, as compared with placebo. These episodes of SGLT2 inhibitors were common, but generally reported to be mild or moderate in intensity, and can be managed with standard treatment, typically without interruption of SGLT2 inhibitor therapy.

Dapagliflozin

Few studies have shown that the high levels of glucosuria induced by SGLT2 inhibitors increase the risk of genital infections and to a relatively lesser extent the risk of urinary tract infections [55-58]. Bailey et al. [59,60] showed the risk of UTI was not increased in SGLT2 initiators compared to DPP-4 initiators. The existing evidence for UTIs related to SGLT2 inhibitors is variable most UTIs were mild to moderate, responded well to treatment with standard antimicrobial treatment

and rarely led to discontinuation of SGLT2 inhibitors**.** We also found the high use of standard antimicrobial therapy with trimethoprim, nitrofurantoin, norfloxacin, and cephalexin. SGLT2 inhibitors have been associated with a higher incidence of genital infections [55]. We found that these infections were more frequent in the SGLT2 than in the DPP-4. Many studies were performed which showed different results regarding the incidence of UTI and genital infection.

Johnsson et al., [61] suggested that Clinical trials using dapagliflozin of 10 mg, the incidence of genital fungal infection were 9.7% among women and 4.2% in men. The incidence of genital fungal infection among patients with a history of genital infections was 25.0%**.** In phase 3 trials, pooled data show that there is a small increase in the incidence of UTI in patients treated with dapagliflozin 5 or 10 mg vs those treated with placebo. However, the incidence was relatively low across all treatment groups (b6%), the rate of infection in the 2.5-mg group was similar to that seen with placebo, and there was no consistent dose-related trend across studies. Generally, the first events of UTI occurred relatively early in the studies. Clinical diagnosis of UTI occurred more commonly in women than in men. The pathogens reported were types commonly seen in patients with type 2 diabetes. Most events were of mild to moderate intensity and resolved with one course of standard antimicrobial treatment.

Glucosuria is a risk factor for the development of UTI, it is important to recognize potential confounding factors. As an example, patients with a history of recurrent UTIs, including patients treated with placebo, experienced much higher rates of UTI during the trials, indicating a predisposition to an infection unrelated to glucosuria. The variation in patient histories with regard to recurrent UTIs limits the ability to generalize findings to the overall patient population. This general pattern also holds true for the relationship between glucosuria and genital infection in dapagliflozin-treated patient says Johnsson et al. [62]. However, the signal for increased risk is clearer for genital infection.

Canagliflozin

According to Nyirjesy et al. [63] in a pooled analysis of trials using canagliflozin in the dose 100 mg and 300 mg, the incidence of genital fungal infections were 10.4% and 11.4% in women and 4.2% and 3.7% in men, respectively. Women with an H/O vulvovaginitis had a higher incidence of treatment-emergent genital fungal infection (29.0%) in the similar analysis. 0.9% and 0.5% of the canagliflozin 100 mg and 300 mg groups, respectively discontinued the therapy due to genital fungal infection**.**

Canagliflozin was generally well tolerated, with specific AEs (e.g. genital mycotic infections, osmotic diuresis-related AEs) that were generally mild to moderate in severity, occurred at a low incidence and infrequently led to discontinuation. While the incidence of UTIs was similar with canagliflozin 100 mg and 300 mg and the control groups (i.e. sitagliptin and placebo/sitagliptin) in a study, a small increase in the occurrence of UTIs was observed with canagliflozin 100 mg (5.9%) compared with canagliflozin 300 mg and placebo (4.3% and 4.0%, respectively. According to Vasilakou et al. [64], the incidence of adverse events was similar with canagliflozin and sitagliptin but the incidence of genital mycotic infection and osmotic diuresis-related AEs was higher with canagliflozin than in the control groups. According to Nyirjesy et al. [65], the incidence of genital mycotic infections was higher in canagliflozin than in placebo. As it has been reported that the adverse events were mild to moderate in intensity and were easily managed with usual therapies and the treatment was continued.

In this study, there was no evidence of either upper or lower tract UTI which is one of the potential risks of the drugs belonging to this class. In vitro studies have reported that glucosuria provides a substrate for bacteria in the urine, and increasing urine glucose levels, in turn, increase the growth rate of potential uro pathogens Despite this, according to Hammar et al., glucose control is not correlated with bacteriuria [66] or symptomatic UTIs [61] in women with diabetes The lack of association of bacteriuria or symptomatic UTIs with canagliflozin therapy supports these findings, indicating that glucosuria is not a risk factor for the development of asymptomatic bacteriuria or UTIs in patients with type 2 diabetes says Geerlings SE et al. [62,67].

According to Nicolle et al., A small increase in the incidence of UTI AEs, including symptomatic UTIs, was consistently observed with canagliflozin compared with control groups, with no dose-dependence observed. Although the incidence of UTI was slightly higher with canagliflozin 100 mg than with canagliflozin 300 mg in Population 1, this was not observed in the larger and broader Population 2 or in the 2 studies in special patient populations. Patients who received canagliflozin tended to have a shorter time to onset of the first symptomatic UTI AE compared with placebo in Population 1; time to onset was similar across treatment groups in Population 2. There was no evidence of an increase in the severity of UTIs with canagliflozin treatment in either population, with most events considered to be mild or moderate in severity. we found that SGLT2 inhibitors increased the incidence of genital tract infections, which was generally attributed to higher glucose levels that were responsible for providing substrate to microorganisms, particularly fungal growth says Nicolle et al., [68]**.** Genital infections and UTIs and remained the most frequent side effects with dapagliflozin, although their incidence tended to decrease over time.

Empagliflozin

According to Roden et al.,[69] Empagliflozin was well tolerated when given as an adjunctive therapy to metformin plus SU. Few studies [70-73] concluded from the data from previous trials, showed that the patients receiving empagliflozin had events with genital infection. Meanwhile, in a proportion of patients with an incidence of UTI, the results were similar between placebo and empagliflozin, but more female patients treated with empagliflozin experienced infections related to the urinary tract.

Hypotension/dehydration/volume depletion

According to Mikhail N. et al., [50] the osmotic diuretic effect of SGLT2 inhibitors may cause some adverse events like fluid depletion in susceptible subjects. Ptaszynska et al., [74] say that in placebo-controlled studies, volume-related events (0.8 vs 0.4 %) occurred slightly more often with dapagliflozin than placebo. However, a similar proportion of patients experienced orthostatic hypotension with dapagliflozin 10 mg versus placebo in hypertensive (6.1 and 6.6 %, respectively) and non-hypertensive (4.0 and 4.2 %) patients based on the data of a systematic review and meta-analysis of RCTs with all SGLT2 inhibitors as said by Baker **[**75].

According to Vasilakou et al., [76] in another systematic review, a high risk of hypotension was found with SGLT2 inhibitors than with other antidiabetic medications (OR = 2.68; 95 % CI 1.14 to 6.29) Zinman et al., [52] said In EMPA-REG OUTCOME, the proportions of patients with adverse events of volume depletion were similar in those patients treated with placebo, empagliflozin 10 mg and empagliflozin 25 mg, in a population with age of 63 years, antecedents of CVD and already treated with various antihypertensive agents (among which 43 % of patients received diuretics)**.** Mikhail et al., [61] say that As the osmotic diuretic effect may cause dehydration, postural hypotension, and dizziness in frail older subjects. Mikhail et al., [77] recommended that in patients on loop diuretics, in case of concerns of volume-related side effects or impaired kidney function.

Conclusions

SGLT2 inhibitors are a class of anti-diabetic agents that act on the proximal tubule of the kidneys. They increase the urinary glucose excretion by inhibiting the sodium-glucose cotransporter, thus reducing the amount of glucose in the blood circulation. As for now, there are three drugs approved by FDA from this class: canagliflozin, dapagliflozin, and empagliflozin. SGLT2 inhibitors have benefits such as weight loss, no hypoglycemic effects, and as it acts on kidneys there are no harmful effects on the pancreas. These beneficial effects are not seen with other class of drugs such as biguanides and sulphonylureas. The main side effects of SGLT2 inhibitors are urinary tract infections, genital infection, diabetic ketoacidosis.

Conflicts of interest

The authors declare no conflict of interest.

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