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Effects of SGLT2 inhibitors on weight loss in patients with type 2 diabetes mellitus

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Abstract. – SGLT2 (sodium-glucose cotransporter type 2) inhibitors are a new class of drugs which reversibly block the glucose reabsorption that occurs in the kidneys. Since their mechanisms of action do not rely on insulin secretion, they constitute a complementary alternative to the classic treatment of type 2 diabetes mellitus. A glycemic level reduction in patients who used SGLT2 inhibitors due to the reversible block of their transporters could be observed. Associated with this, there was a reduction in body weight and blood pressure (BP) caused by osmotic diuresis. Few adverse effects and low drug interaction combined with antihyperglycemic effects are some of the benefits of these inhibitors widely discussed in clinical trials. Patients with history of urogenital infections or those on diuretics must be carefully evaluated before the administration of these drugs. While a promising class of drugs indicated as a treatment for patients with type 2 diabetes mellitus, SGLT2 inhibitors should not be prescribed for individuals with severe renal or hepatic impairment. Therefore, as there are only a few situations in which they should not be indicated, the efficacy, safety and tolerability of these inhibitors allow them to be used in a wide range of patients. Nevertheless, further researches are required so that the possible long-term risks can be studied and the benefits associated with their use can be more objectively elucidated.

Key Words:
Sodium-glucose transporter 2, Diabetes mellitus, T2DM, Weight loss, Hyperglycemia.

Introduction

Diabetes mellitus is a multifactorial chronic metabolic disease that affects 347 million people worldwide[1]. By the year 2035, this number is forecasted to reach 592 million[2]. Since the prevalence rate of diabetes mellitus among the population aged 20-79 years in countries like the United States, India, Brazil and China is of 9.4%, 9.1%, 8.7% and 8.6% respectively, the disease stands as a major world public health issue[3]. As the disease progresses, cardiovascular, renal, ocular and neurological complications may occur, thus reducing patients' life expectancy by years[2].

Type 2 diabetes mellitus (T2DM) is the most frequent form of the disease, representing 90% of the diagnosed events. In such cases, there is a higher tissue resistance to insulin action, which makes the pancreas release more insulin as a compensatory mechanism. With time, this increased production becomes insufficient to keep blood glucose at normal levels[4].

T2DM is strongly related to obesity, a condition that has become more and more common throughout the world. The accumulation of visceral fat leads to the reduction of hepatic insulin clearance with a resultant hepatic neoglucogenesis[3,5]. Therefore, as obesity is a high-risk factor for T2DM, its control is of utmost importance[6].

Whenever changes in lifestyle behaviors, such as the practice of regular physical exercises and a proper diet management, are not enough for the disease control, additional pharmacological treatments are recommended. SGLT2 (sodium-glucose cotransporter type 2) inhibitors like canagliflozin, dapagliflozin, empagliflozin and ipragliflozin are just some examples of what is available today[7-9].

In the kidneys, the filtered glucose can be reabsorbed into the blood by means of two different transporters, namely SGLT1 and SGLT2[10].

The density of SGLT1 is higher in the distal third (S3 segment) of the proximal convoluted tubule of the nephron[11]. It is also expressed, in smaller quantities, in the small intestine, in the trachea and the heart[10]. Physiologically speaking, it plays a minor role in the reabsorption of glucose (10%). SGLT2, on the other hand, is densely located in the proximal third (S1 segment) of the proximal convoluted tubule, especially in the renal cortex, and it plays a major role in the reabsorption of the glucose (90%)[11].

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Therefore, the reversible inhibition of SGLT2 prevents excessive blood glucose from returning to the circulatory system, and this surplus is eliminated through the urine. As a consequence, glycemia is reduced in diabetic patients[12].

This review aims not only to evaluate the results of SGLT2 inhibitors in the control of type 2 diabetes and the induction of weight loss in patients with such condition, but also to include data on its safety, efficacy and tolerability.

Pharmacokinetics and Pharmacodynamics of SGLT2 Inhibitors

Owing to the fact SGLT2 inhibitors do not depend on pancreatic endocrine secretion, they can be used in monotherapies, or co-administered with oral antidiabetics already prescribed in clinical practice[13-15].

Some of the pharmacokinetic data of the studied medications are shown in Table I.

Although SGLT2 is responsible for the reabsorption of 90% of the glomerular glucose, its inhibitors can only suppress 30-50% of this total. This may occur due to the fact that these drugs are actively eliminated/reabsorbed in the same site where they act, thus reducing the variety of blocked transporters along the proximal tubule[19]. Therefore, SGLT2 antisense oligonucleotides, which suppress SGLT2 mRNA expression in up to 80%, showed having a much greater effect on glucose elimination in several species, such as rats and monkeys[20].

Table II summarizes the main positive and negative aspects, confirmed or not by conducted studies.

Adverse Effects and Administration in Patients with Renal and Hepatic Dysfunction

Besides weight loss, another advantage SGLT2 inhibitors have over traditional antidiabetic medications is the low prevalence and intensity rates of adverse effects (AE). With the use of drugs like glipizide, the occurrence of hypoglycemic events among patients reaches rates of 45.3%, whereas with the use of SGLT2 inhibitors in monotherapy, this rate stays close to placebo levels[35,36]. However, many studies have revealed a higher prevalence of genital infections (GI) and urinary tract infections (UTI), especially among females, when such inhibitors are administered[37]. The intensity of the reported UTIs ranged from mild to moderate, and they were easily treated with traditional antimicrobials.

Despite the fact most of the cases were reported in patients with a history of recurrent UTIs (17.1-21.1%), they did not seem to be dose-dependent on the new class of drugs[38]. When it came do GIs, they manifested as vaginal infections, vulvovaginal mycotic infections and vaginal candidiasis in females and as balanitis in males. In patients without a history of GIs, the prevalence was slightly higher in those who made use of dapagliflozin in relation to the

Table I. Main Pharmacokinetic Features of the Inhibitors. UGE: Urinary Glucose Excretion; N/r: Not reported.

	Canagliflozin	Dapagliflozin	Empagliflozin	Ipragliflozin
Bioavailability	65%[9]	78%[9]	> 60%[17]	65%[9]
UGE (g/day)	51.4[16]	40.8[16]	30.6[19]	90[8]
Therapeutic doses	100-300 mg[17]	5.0-10.0 mg[17]	10-25 mg[17]	25-50 mg[17]
Binding rate with plasma transporter	98%[17]	91%[17]	86%[17]	N/r
Metabolization	Glucuronidation reaction through the enzyme O-glucoronidase (2 inactive metabolites – M5 and M7)[6]	Glucuronidation reaction in inactive conjugates (dapagliflozin 3-O-glucuronide)[16]	Glucuronidation (predominantly) and oxidation reactions in 6 inactive metabolites[17]	Glucuronidation reaction in inactive metabolites – M1, M2, M3, M4 and M6[19]
Elimination pathway	Urine and feces; < 1% of unaltered drug eliminated in urine[17]	Inactive metabolites eliminated in urine; < 2% of unaltered drug eliminated in urine[17]	Eliminated through urine and feces; 28.6% of the unaltered drug iseliminated in urine[17]	Mainly through urine by inactive metabolites; < 1% of unaltered drug eliminated in urine[17]
Approval and development	40 countries, including EU, USA and Japan[9]	40 countries, including EU, USA, China and Russia[9]	FDA approved[18]	Approved in Japan[9]

Table II. Positive and negative effects, confirmed or not, of SGLT2 inhibitors. HDL-C: HDL-cholesterol.

	Positive aspects	Negative aspects
Confirmed	1. Do not depend on pancreatic β-cell functions, and they can be used in all stages of the disease[13] 2. Cause a decrease in arterial systolic pressure[21,22] 3. Have minimum hypoglycemic potential[9] 4. Reduce arterial stiffness[23] 5. Cause weight loss[22] 6. Have low drug interaction with oralantidiabetics, antihypertensives, and inducers and inhibitors of cytochrome P450 enzymes[23-27] 7. Can be used in monotherapies or as complementary therapies along with antidiabetics[14,15,28]	1. Higher prevalence of urinary tract and genital infections[9] 2. Increase in osmotic diuresis[22] 3. Great precaution when used in patients with moderate to severe renal insufficiency[31]
Unconfirmed (under consideration)	1. Increase in HDL-C serum levels[29] 2. Presumed prophylactic effect against the accumulation of triacylglycerols in the liver and the formation of fat clusters[30]	1. Increased risk of bone fracture, causing alterations in the homeostasis of calcium and phosphate (secondary hyperparathyroidism induced by high phosphate reabsorption)[32] 2. Possible association between use and the occurrence of diabetic ketoacidosis[34]

placebo. On the other hand, in those with a history of GIs, the incidence sharply increased (23-50%) in relation to the placebo (10%). For this reason, the administration of SGLT2 inhibitors should be avoided in patients with this profile[39].

Another aspect to be considered is the possible relation between the use of these novel drugs and a higher prevalence of urinary bladder and breast cancer[40]. In 2012, the U.S. Food and Drug Administration (FDA) rejected the approval of dapagliflozin due to the fact a study revealed 9 cases of bladder cancer among 4310 patients who received the medication versus 1 case among the 1962 patients who received placebo[41]. Nevertheless, it is important to point out that before the treatment, many of the diagnosed patients already presented hematuria, raising the hypothesis of a pre-existing condition that was not triggered by the medication[40].

Additionally, despite the low occurrence and severity of the AE experienced by patients, dysfunctions and previous or concomitant pathologies may interfere with the metabolism of the drugs. Renal failure was evaluated in order to measure the efficacy and pharmacokinetic patterns that would not be in consonance with their normal values. From what was observed, in the case of moderate and severe renal dysfunction, the efficacy of these drugs was mildly reduced and the elimination of their metabolites M5 and M7 was of greater difficulty. However, these compounds are biologically inactive, and they apparently do not cause any additional organic alterations[42,43].

To verify the possible risks of these new drugs, administration to patients with mild to severe hepatic impairment (HI) was compared with the administration to healthy individuals. First, when the use of dapagliflozin was analyzed, a total of 24 patients (6 with mild HI, 6 with moderate cases, 6 with severe cases and 6 healthy individuals) made use of 10 mg of the medication in a single daily dose. Maximum plasma concentration levels and bioavailability showed no significant differences in the 3 categories of HI in relation to healthy individuals. Adverse effects were balanced in the 4 groups, ranging from mild to moderate intensities. On the other hand, the risk caused by the long-term use of dapagliflozin in patients with HI, especially in severe cases, is still unknown due to the few number of studies on the subject available in the literature[44]. A similar trial was carried out with canagliflozin, consisting of 8 patients with mild HI, 8 with moderate cases and 8 healthy individuals. Differences involving the same variables from the previous study were also minimal and not clinically relevant. Interestingly, there was a slight increase in these parameters regarding its inactive metabolites (M5 and M7). This fact may indicate a re-

duction of the biliary clearance, which justifies the decrease of these compounds in the fecal excretion. Yet, owing to the fact they are inactive, they showed no clinical significance. Since this study did not include patients with severe HI, the use of canagliflozin among this share of the population is not recommended[42].

A single 50 mg dose of empagliflozin was administered to 36 patients (12 healthy individuals, 8 with mild, 8 with moderate and 8 with severe HI). Upon comparing the maximum plasma concentration levels and bioavailability in patients with HI in relation to the healthy ones, it was observed that, although these parameters gradually increased according to the HI level, they did not even double their physiological values. This showed that the drug was well tolerated, no matter what the HI level was, with no need for dose alteration. Six cases of AE in the healthy patients group, three in the moderate HI group and two in the severe HI group were reported, and all of them ranged from mild to moderate intensity[45].

Finally, when it came to ipragliflozin (100 mg single dose), other pharmacokinetic parameters were evaluated, like half-life time and plasma binding rate in 2 groups of 16 patients divided as follows: 8 healthy individuals and 8 with moderate HI. There were no relevant clinical changes when such parameters in both groups were compared, neither in regard to ipragliflozin nor in regard to its main metabolite M2. Both were well tolerated in the two groups[19].

FDA has recently reported a possible relation between the use of SGLT2 inhibitors and a higher occurrence of diabetic ketoacidosis. This condition is characterized by an increase in the concentration of hepatic ketone bodies, which are used by tissues that require energy substrate due to a higher resistance to insulin. As these compounds have an acidic property, they reduce blood pH, thus resulting in the onset of many symptoms. Therefore, if patients under treatment present symptoms like tachypnea, nausea, vomiting, abdominal pain, mental confusion or excessive drowsiness, they should immediately request medical assistance. In case diagnosis is confirmed, the treatment with SGLT2 inhibitors must be discontinued[34,46].

A total of 20 cases of ketoacidosis in patients under treatment with canagliflozin, dapagliflozin and empagliflozin were reported from March 2013 to June 2014. Symptoms were first noticed 2 weeks after the beginning of the therapy with these drugs, and all of them needed to be hospitalized so that their condition could be monitored. Nearly half of the cases of ketoacidosis were possibly related to acute illnesses (influenza viral infections, gastroenteritis, UTIs and traumas), decrease in food and fluid intake and a reduction in insulin administration. The other half, however, did not seem to be associated with any pre-existing condition. New studies are currently being investigated so that these safety issues can be better elucidated[34].

Cardiovascular Outcomes Brought by the Administration of SGLT2 Inhibitors

Many epidemiological and physiopathological evidences point to T2DM as an important condition that increases the risk of cardiovascular events. In the United States, deaths caused cardiovascular diseases are 1.7-fold higher in diabetic than in non-diabetic patients. Furthermore, the rates of hospital admissions for cardiac ischemia and cerebrovascular accidents (CVA) are respectively 80% and 50% higher in the diabetic population[47].

Endothelial injury and vascular dysfunction, two events that occur due to the lack of glycemic control and disturbances in the synthesis of reactive oxygen species, are the primary mechanisms responsible for the increase in cardiovascular risks in diabetic individuals[48]. They create conditions for the installation of an inflammatory process, which favors the infiltration of macrophages in the outer layers of arteries, expanding atherosclerosis, one of the microvascular complications of the disease[48]. According to a study that included 4209 patients with T2DM over a period of 10 years, the adequate glycemic control prevents the imbalance of this process, thus contributing to decrease the risk of AMI or death by any cause[49].

Given the relevance of SGLT2 inhibitors in the treatment of T2DM, studies that evaluate the safety features and risks of these drugs, as well as the possible cardiovascular benefits they may provide, are of utmost importance. Modest improvements in cardiovascular risk factors, like the reduction of blood pressure (BP), body weight and waist circumference have been described since pre-clinical studies[40]. However, very few convincing evidences of a reduction in mortality rate or a decrease in the prevalence of cardiovascular diseases caused by the use of these drugs have been shown so far[50]. Recently, the number of studies on the cardiovascular results in therapies with SGLT2 inhibitors has been increasing significantly.

Cardiovascular evidences observed in trials with animals reveal that these drugs exert a preventive effect on artery rigidity, atherosclerosis[51], coronary wall thickness, endothelial dysfunction and alterations in cardiac superoxide levels of diabetic rats[52]. The use of dapagliflozin in diabetic rats also showed an alteration in calcium ion transport to the ventricular cardiomyocytes, producing a negative inotropic effect[53].

In a report published by the Canadian Agency for Drugs and Technology in Health in November 2015, nine reviews on the use of currently approved SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) and other antihyperglycemic agents (glimepiride, glipizide, metformin and sitagliptin) were compared in relation to their cardiovascular effects. The results found in this study showed that besides glycemic control, SGLT2 inhibitors significantly reduced arterial rigidity, vascular resistance and systolic and diastolic BP[54]. BP reduction is explained by the sum of several positive effects, like the greater diuretic action, the remodeling of kidney microcirculation, the reduction of artery rigidity and the effects generated by weight loss and waist fat reduction[23].

Although the described results have been confirmed overall, the first studies focusing directly on the evaluation of cardiovascular effects brought by the administration of SGLT2 inhibitors are still in progress.

In November 2015 a study known as EMPA-REG OUTCOME was published, confirming a significant reduction in cardiovascular morbidity and mortality rate in patients on empagliflozin[55]. It included 7020 patients who were followed up during a mean time of 3.1 years. The patients were divided into 3 groups, namely placebo, empagliflozin 10 mg and empagliflozin 25 mg. All recruited participants had previous known cardiovascular disease, and they had not received any antihyperglycemic medication for at least 12 weeks. The primary endpoint was defined as the occurrence of death by cardiovascular events or non-fatal infarction or CVA; the secondary endpoint was the primary composite endpoint plus some hospital admissions due to unstable angina cases. Right after the beginning of the trial, between months 3 and 6 to be exact, some statistically significant reductions in mortality from any cause or from cardiovascular causes in the group on medication could be observed when compared with the placebo group. This trend remained significant throughout the study, so much so that at the end of the study the primary endpoint was observed in 10.5% of the medication group and 12.1% of the placebo group. The reduction of deaths from cardiovascular causes was of 3.7% for empagliflozin and 5.9% for placebo (hazard ratio, 0.62); hospital admission rate due to cardiovascular causes was also lower in the empagliflozin group (2.7% *vs.* 4.1% placebo). Regarding the prevalence of cerebral and myocardial ischemic events, there were no significant differences between both groups[55].

The 10- and 25-mg doses of empagliflozin resulted in different metabolic effects, but the hazard ratios for the cardiovascular outcomes were similar. Therefore, the use of different doses in clinical practice will especially depend on the need of metabolic reduction and the prevalence of AEs. Interestingly, the study also revealed that 47.4% of the placebo-group patients needed to have their antihypertensive therapy complemented, whereas in the empagliflozin group the rate was only 40.6%[55].

The evaluation of cardiovascular outcomes for patients on canagliflozin is still in progress with 3 major ongoing trials: CANVAS, CANVAS-R and CREDENCE. The 2 last ones will also analyze renal effects, and the 3 of them are expected to be published between 2017 and 2019[50].

Nevertheless, the use of canagliflozin has already shown positive results in the reduction of plasma uric acid concentrations in up to 13% of T2DM patients[56]. The relation between uric acid and cardiovascular risk is explained by several mechanisms. The increase in its plasma concentration induces hypertension due to a greater renal vasoconstriction and the activation of the renin-angiotensin-aldosterone system. Uric acid also participates in the aggravation of atherosclerosis by the induction of endothelial injury and inflammation[57].

Finally, cardiovascular outcomes caused by the use of dapagliflozin are being analyzed in a trial known as DECLARE-TIMI 58, planned to be published in April, 2019[50]. Nonetheless, BP reduction by dapagliflozin is a known fact. In a phase III study that compared the effects of dapagliflozin on blood pressure reduction in diabetic and hypertensive patients, there was a difference of -4.28 mmHg between the group on dapagliflozin and a renin-angiotensin-aldosterone system blocker and the group on an antihypertensive alone[58]. Moreover, it has been suggested that the use of dapagliflozin can also reduce diabetic

nephropathy progression owing to the anti-inflammatory remodeling of the kidney microcirculation, which explains the nephroprotective action[59].

Relation Between the Efficacy of SGLT2 Inhibitors and Weight Loss

This new class of drugs seems to act on the two great pillars on which the conventional treatment is based: glycemia reduction and weight loss[60]. The former occurs as a direct consequence of SGLT2 inhibition, increasing urinary glucose excretion by up to 80 g/day. This not only contributes to the glycemic control, but also helps improve possible comorbidities related to diabetes, like cardiovascular diseases and peripheral neuropathies[61-63]. Studies with patients who had mean HbA1c levels greater than 8% and were treated with canagliflozin, dapagliflozin and empagliflozin revealed a reduction in those levels to less than 7% in 64% (*versus* 32% placebo), 41% (*versus* 26% placebo) and 32% (*versus* 9% placebo) of the cases respectively[64]. Regarding ipragliflozin, a 12-week study with 50 mg daily doses showed a reduction of 0.66% in HbA1c levels and of 0.66 kg when compared with the placebo group[8]. Other trials with dapagliflozin and canagliflozin reported not only a reduction of 12-32% in HbA1c levels, but also a decrease of up to 5 mmHg in resting BP. Since both conditions are commonly associated, these findings suggest a possible benefit to diabetic and hypertensive patients[23,65-67].

Weight loss, on the other hand, can be considered an indirect effect resultant from the renal excretion of glucose. However, it is important to define the etiology of this weight decrease. In other words, it is necessary to answer the following questions: did the caloric deficit caused by glucose elimination induce a higher lipid catabolism with a consequent body mass loss? Did glucose, more concentrated in the glomerular filtrate, promote higher water retention in the urine, which constituted the weight effectively lost? Was the resultant weight loss a combination of both factors[68,69]? To answer these questions, a 24-week study comparing 2 groups was carried out: one that made use of placebo and metformin, and another that made use of dapagliflozin 10 mg and metformin. The first obtained result was a more intense polyuria in the second group, which contributed to a greater fluid loss. By the end of the study, waist circumference and fat mass index were analyzed, and the following results were found: regarding waist circumference, placebo group = -0.99 cm and dapagliflozin group = -2.51 cm; as to fat mass index, placebo group= -0.74 kg and dapagliflozin group = -2.22 kg. The conclusion was that weight loss occurred due to the confluence of both theorized factors, but each factor prevails at different moments[68]. Another result revealed in the study was that there was a great reduction in a visceral fat deposition; therefore, the use of these drugs as a prophylactic method to treat hepatic steatosis could be of great help[31,68]. The average proportional weight loss measured for dapagliflozin and canagliflozin stands between 1 and 3%, while other reports mention a loss greater than 5% of total body mass[12,66,67].

According to the analysis of the conducted studies, weight loss was perceptible after week 6, a period when there was a slight increase in urine flow induced by the osmotic diuresis[64]. From that moment on, weight loss gradually slowed down, and it was stabilized between weeks 26 and 34. In the period that followed, there was a relative steadiness in value, with a sporadic tendency of weight gain[35,64,70]. In a 2-year study, which involved the administration of both dapagliflozin (2.5-10 mg) and metformin, weight loss stabilization occurred around week 26, with a reduction of approximately 3.0 kg of mass over this period of time[35]. In a different study, which compared such parameters between empagliflozin 10 mg, empagliflozin 25 mg and metformin, stabilization was observed around week 12, with a lower average weight loss value (approximately 2.1 kg). Moreover, it is interesting to compare this average in the monotherapy administration of empagliflozin with the complementary metformin in this case. First, weight loss was 2.1 kg as seen before, whereas, in the co-administration, the average value was 3.3 kg. These differences remained significant throughout the 90-week study[70].

Among the analyzed SGLT2 inhibitors, ipragliflozin showed a lower average of body mass reduction, with mean values of -1.75 kg for doses of 20 mg and 50 mg[71]. However, on account of the short duration of the trial and the small number of specific studies on this drug, it is more likely that its efficacy will be better measured as new publications on the theme come out.

Yet, new findings suggest that SGLT2 inhibitors contribute to the reduction of the risk of diabetic nephropathy[43]. In cases of decompensat-

Table III. Selected studies comparing effects of SGLT2 inhibitors in body measure, glycemic index and blood pressure parameters.

Study	Sample	Effects	Adverse effects
DAPA 2.5-10 mg + metformin *versus* glipizide 5-20 mg + metformin (52 weeks)[72]	814 patients (406 DAPA + metformin *vs.* 408 glipizide + metformin)	Weight; kg (-3.22 *vs.* +1.44) HbA1c; % (-0.52 *vs.* -0.52) FPG N/r; SAP N/r	Hypoglycemia; % (3.4 *vs.* 39.6) UTI; % (10.8 *vs.* 6.4) GI; % (12.3 *vs.* 2.7)
DAPA 2.5-10 mg + metformin *versus* glipizide 5-20 mg + metformin (104 weeks)[35]	814 patients (406 DAPA + metformin *vs.* 408 glipizide + metformin)	Weight; kg (-3.7 *vs.* +1.4) HbA1c; % (-0.32 *vs.* -0.14) FPG; mmol/L (-1; 12 *vs.* -0.68) SAP; mmHg (-2.7 *vs.* +1.2)	Hypoglycemia; % (4.2 *vs.* 45.8) UTI; %(13.5 *vs.* 9.1) GI; % (14.8 *vs.* 2.9)
Placebo + metformin *versus* DAPA 5.0 mg + metformin *versus* DAPA 10.0 mg + metformin (48 weeks)[36]	546 patients (137 placebo + metformin *vs.* 137 DAPA 2.5 + metformin *vs.* 137 DAPA 5.0 + metformin *vs.* 135 DAPA 10 + metformin)	Weight; kg (-0.40 *vs.* -2.92 *vs.* -2.65) HbA1c; % (-0,31 *vs.* -0.65 *vs.* -0.67 *vs.* -0.82) FPG; mmol/L (-0.29 *vs.* -0.95 *vs.* -1.15 *vs.* -1.23) SAP reported only for 102 weeks	Reported only for 102 weeks
Placebo + metformin *versus* DAPA 5.0 mg + metformin *versus* DAPA 10.0 mg + metformin (102 weeks)[36]	546 patients (137 placebo + metformin *vs.* 137 DAPA 2.5 + metformin *vs.* 137 DAPA 5.0 + metformin *vs.* 135 DAPA 10 + metformin)	Weight; kg (+1.36 *vs.* 1.10 *vs.* - -1.70 *vs.* -1.74) HbA1c; % (+0.02 *vs.* -0.48 *vs.* -0.58 *vs.* -0.78) FPG; mmol/L (-0.58 *vs.* -1.07 *vs.* -1.47 *vs.* -1.36) SAP; mmHg (+1.5 *vs.* +0.7 ($p = 0.1111$) *vs.* -1.1 *vs.* -0.3)	Hypoglycemia; % (5.8 *vs.* 3.6 *vs.* 5.1 *vs.* 5.2) UTI; % (8.0 *vs.* 8.0 *vs.* 8.8 *vs.* 13.3) GI; % (5.1 *vs.* 11.7 *vs.* 14.6 *vs.* 12.6)
Placebo + glimepiride *versus* DAPA 2.5 mg + glimepiride *versus* DAPA 5.0 mg + glimepiride *versus* DAPA 10 mg + glimepiride (48 weeks)[74]	596 patients (146 placebo + glimepiride *vs.* 154 DAPA 2.5 + glimepiride *vs.* 145 DAPA 5 + glimepiride *vs.* 151 DAPA 10 + glimepiride)	Weight; kg (-0.77 *vs.* -1.36 *vs.* -1.54 *vs.* -2.41) HbA1c; % (-0.04 *vs.* -0.41 *vs.* -0.56 *vs.* -0.73) FPG; mmol/L (+0.14 *vs.* -0.93 *vs.* -0.92 *vs.* -1.66) SAP N/r	Hypoglycemia; % (6.8 *vs.* 9.7 *vs.* 10.3 *vs.* 11.3) UTI; % (7.5 *vs.* 4.5 *vs.* 7.6 *vs.* 7.9) GI; % (1.4 *vs.* 5.2 *vs.* 6.2 *vs.* 8.6)
Placebo + insulin up to 30 units/day ± up to 2 oral antidiabetics (OAD) *versus* DAPA 2.5 mg + insulin ± OAD *versus* DAPA 5.0 mg + insulin ± OAD *versus* DAPA 10 mg + insulin ± OAD (48 weeks)[14]	800 patients (193 placebo *vs.* 202 DAPA 2.5 *vs.* 211 DAPA 5.0 *vs.* 194 DAPA 10.0)	Weight; kg (+0.82 *vs.* -0.96 *vs.* -1.00 *vs.* -1.61) HbA1c; % (-0.47 *vs.* -0.79 *vs.* -0.96 *vs.* -1.01) FPG; mmol/L (N/r *vs.* -0.69 *vs.* -0.90 *vs.* -0.94) insulin dose; units/day (+10.54 *vs.* -0.92 *vs.* -0.30 *vs.* -0.70) SAP; mmHg (-1.49 *vs.* -5.30 *vs.* -4.33 *vs.* -4.09)	Hypoglycemia; % (51.8 *vs.* 60.4 *vs.* 55.7 *vs.* 53.6) UTI; % (5.1 *vs.* 7.9 *vs.* 10.8 *vs.* 10.2) GI; % (2.5 *vs.* 6.4 *vs.* 9.9 *vs.* 10.7)
Placebo + exercises and diet (ED) *versus* DAPA 2.5 mg + ED *versus* DAPA 5.0 mg + ED *versus* DAPA 10 mg + ED (24 weeks)[76]	485 patients (75 placebo *vs.* 65 DAPA 2.5 *vs.* 64 DAPA 5 *vs.* 70 DAPA 10); morning measurement; remaining samples were measured in the afternoon	Weight; kg (-2.2 *vs.* -3.3 *vs.* -2.8 *vs.* -3.2) HbA1c; % (-0.23 *vs.* -0.58 *vs.* -0.77 *vs.* -0.89) FPG; mg/dL (-4.1 *vs.* -15.2 *vs.* -24.1 *vs.* -28.8) SAP; mmHg (-0.9 *vs.* -2.8 *vs.* -1.7 *vs.* -2.0); similar effects were observed in afternoon measurements	Hypoglycemia; % (2.7 *vs.* 1.5 *vs.* 0.0 *vs.* 2.9) UTI; % (4.0 *vs.* 4.6 *vs.* 12.5 *vs.* 5.7) GI; % (1.3 *vs.* 7.7 *vs.* 7.8 *vs.* 12.9); similar occurrence of adverse effects in afternoon measurements
CANA 300 mg ± metformin and sulphonylureas *versus* sitagliptin 100 mg ± metformin and sulphonylureas (52 weeks)[29]	755 patients (377 CANA 300 *vs.* 378 sitagliptin 100)	Weight; kg (-2.3 *vs.* +0.1) HbA1c; % (-1.03 *vs.* -0.66) FPG; mmol/L (-1.7 *vs.* -0.3) SAP; mmHg (-5.1 *vs.* -0.9)	Hypoglycemia; % (43.2 *vs.* 40.7) UTI; % (4.0 *vs.* 5.6) GI; % (24.5 *vs.* 4.8)

Table Continued

Table III *(Continued)*. Selected studies comparing effects of SGLT2 inhibitors in body measure, glycemic index and blood pressure parameters.

Study	Sample	Effects	Adverse effects
CANA 100 mg monotherapy *versus* CANA 100 mg + sulphonylurea *versus* CANA 100 mg + glinide *versus* CANA 100 mg + inhibitor of α-glucosidase *versus* CANA 100 mg + thiazolidinedione *versus* CANA 100 mg + DPP-4 inhibitor (52 weeks)[37]	584 patients (127 CANA monotherapy *vs.* CANA + sulphonylurea *vs.* CANA + glinide *vs.* CANA + inhibitor of α-glucosidase *vs.* CANA + biguanide *vs.* CANA + thiazolidinedione *vs.* CANA + DPP-4 inhibitor)	Weight; % (-4.42 *vs.* -2.94 *vs.* -3.97 *vs.* -4.03 *vs.* -4.42 *vs.* -3.37 *vs.* -4.00) waist circumference; cm (-2.76 *vs.* -1.96 *vs.* -2.93 *vs.* -2.27 *vs.* -3.40 *vs.* -3.12 *vs.* -3.34) HbA1c; % (-0.75 *vs.*-0.96 *vs.* -1.06 *vs.* -0.91 *vs.* -0.87 *vs.* -1.04 *vs.* -1.04) FPG; mg/dL (-24.2 *vs.* -29.3 *vs.* 32.1 *vs.* -26.8 *vs.* -28.5 *vs.* -34.5 *vs.* -37.5) SAP; mmHg (-3.82 *vs.* -4.55 *vs.* -4.72 *vs.* -6.35 *vs.* -6.46 *vs.* -2.84 *vs.* -5.45)	Hypoglycemia; % (6.3 *vs.* 17.7 *vs.* 6.2 *vs.* 0.0 *vs.* 5.6 *vs.* 4.8 *vs.* 4.2) UTI; % (1.6 *vs.* 4.0 *vs.* 1.5 vs 6.5 *vs.* 2.8 *vs.* 1.6 *vs.* 5.6) GI; % female/male (5.0/1.1 *vs.* 9.1/0.0 *vs.* 0.0/0.0 *vs.* 10.0/3.8 *vs.* 13.3/0.0 *vs.* 17.6/0.0)
CANA 100 mg + placebo *versus* CANA 300 mg + placebo (18 weeks)[15]	2072 patients (692 CANA 100 + placebo *vs.* 690 CANA 300 + placebo *vs.* 690 only placebo)	Weight; % CANA100/CANA300 (-1.9 *vs.* -2.4) HbA1c; % CANA100/CANA300 (-0.62 *vs.* -0.73) FPG; mmol/L CANA100/ CANA300 (-1.2 *vs.* -1.6) SAP; mmHg (-2.3 *vs.* -4.1)	Reported only for 52 weeks
CANA 100 mg + placebo *versus* CANA 300 mg + placebo (52 weeks)[15]	2072 patients (692 CANA 100 + placebo *vs.* 690 CANA 300 + placebo *vs.* 690 only placebo)	Weight; % CANA100/CANA300 (-2.8 *vs.* -3.5) HbA1c; % CANA100/CANA300 (-0.58 *vs* .-0.73) FPG; mmol/L CANA100/ CANA300 (-1.1 *vs.* -1.5) SAP; mmHg CANA100/CANA300 (-3.1 *vs.* -6.2) insulin doses; units/day placebo/CANA100/ CANA300 (+4.4/-2.0/-4.3)	Hypoglycemia; % placebo/ CANA100/CANA300 (48.2/59.1/57.3) UTI; % placebo/CANA100/CANA300 (5.7/5.7/6.0) GI; % placebo/ CANA100/CANA300 (2.0/10.9/12.6)
Placebo *versus* CANA 50 mg *versus* CANA 100 mg *versus* CANA 200 mg *versus* CANA 300 mg *versus* CANA 300 mg/twice a day (x2) *versus* sitagliptin 100 mg (12 weeks)[77]	451 patients (65 placebo *vs.* 64 CANA50 *vs.* 64 CANA100 *vs.* 65 CANA200 *vs.* 64 CANA300 *vs.* 64 CANA 300 x2 *vs.* 65 sitagliptin)	Weight; kg (-1.1 *vs.* -2.3 *vs.* -3.6 *vs.* -2.7 *vs.* -3.4 *vs.* -3.4 *vs.* -0.6) HbA1c; % (-0.22 *vs.* -0.79 *vs.* -0.76 *vs.* -0.70 *vs.* -0.92 *vs.* -0.95 *vs.* -0.74) FPG; mg/dL (+3.6 *vs.* -16.2 *vs.*-25.2 *vs* .-27.0 *vs.* -25.2 *vs.* -23.4 *vs.* -12.6) SAP; mmHg (-1.3 *vs.* -0.9 *vs.* + 1.0 *vs.* -2.1 *vs.* -4.9 *vs.* -3.6 *vs.* -0.8)	Hypoglycemia; % (1.5 *vs.* 0.0 *vs.* 1.5 *vs.* 6.2 *vs.* 0.0 *vs.* 3.1 *vs.* 4.6) UTI; % (7.6 *vs.* 9.3 *vs.* 9.3 *vs.* 2.5 *vs.* 9.3 *vs.* 7.8 *vs.* 6.1) GI; 1 % (1.5 *vs.* 7.8 *vs.* 6.2 *vs.* 3.1 *vs.* 3.1 cs 6.2 *vs.* 1.5)
Metformin *versus* EMPA 10 mg *versus* EMPA 10 mg + metformin *versus* EMPA 25 mg *versus* EMPA 25 mg + metformin *versus* sitagliptin + metformin (78 weeks)[70]	659 patients (56 metformin *vs.* 80 EMPA 10 *vs.* 137 EMPA 10 + metformin *vs.* 88 EMPA 25 *vs.* 139 EMPA 25 + metformin *vs.* 56 sitagliptin + metformin)	Weight; kg (-1.3 *vs.* -2.2 *vs.* -3.1 *vs.* -2.6 *vs.* -4.0 *vs.* -0.4) Waist circumference; cm (-0.2 *vs.* -3.0 *vs.* -1.9 *vs.* -2.2 *vs.* -2.4 *vs.* +0.04) HbA1c (-0.56 *vs.* -0.34 *vs.* -0.34 *vs.* -0.47 *vs.* -0.63 *vs.* -0.40) FPG; mg/dL (-26 *vs.* -30 *vs.* -21 *vs.* -28 *vs.* -32 *vs.* -16) SAP; mmHg (+2.0 *vs.* +0.1 *vs.* -3.3 *vs.* -1.7 *vs.* -3.0 *vs.* +1.8)	Hypoglycemia; % (3.6 *vs.* 0.9 *vs.* 1.8 *vs.* 1.8 *vs.* 2.4 *vs.* 12.5) UTI; % (3.6 *vs.* 3.8 *vs.* 9.0 *vs.* 6.4 *vs.* 12.7 *vs.* 12.5) GI; % (4.7 *vs.* 3.0 *vs.* 5.5 *vs.* 3.6 *vs.* 1.8 *vs.* 0.0)
Placebo *versus* IPRA 12.5 mg *versus* IPRA 25 mg *versus* IPRA 50 mg *versus* IPRA 100 mg (12 weeks)[71]	360 patients (69 placebo *vs.* 73 IPRA 12.5 *vs.* 74 IPRA 25 *vs.* 72 IPRA 50 *vs.* 72 IPRA 100)	Weight; kg (-0.39 *vs.* -1.46 *vs.* -1.69 *vs.* -1.81 *vs.* -2.10) HbA1c; % (+0.50 *vs.* -0.11 *vs.* -0.47 *vs.* -0.79 *vs.* -0.81) FPG; mg/dL (+12.0 *vs.* -15.6 *vs.* -23.7 *vs.* -34.1 *vs.* -46.9) SAP N/r	Hypoglycemia; % (0.0 *vs.* 0.0 *vs.* 0.0 *vs.* 0.0 *vs.* 1.3) UTI; % (1.4 *vs.* 0.0 *vs.* 0.0 *vs.* 4.1 *vs.* 1.3) GI; % (0.0 *vs.* 1.3 *vs.* 0.0 *vs.* 1.3 *vs.* 1.3)

DAPA: dapagliflozin; CANA: canagliflozin; EMPA: empagliflozin; IPRA: ipragliflozin; N/r: Not reported; FPG: Fasting Plasma Glucose; UTI: Urinary Tract Infection; GI: Genital infection.

ed diabetes, hyperglycemia favors an increased reabsorption of glucose through SGLT2. This reduces the available solute concentration in the glomerular filtrate as it flows through the macula densa, inhibiting the tubuloglomerular feedback mechanism, thus resulting in a higher filtration rate in each single nephron[72]. This hyperfiltration, associated with a hyperglycemic condition, constitutes a major risk factor for nephropathy, which affects up to 40% of diabetic patients[43]. Upon administering SGLT2 inhibitors, proximal filtration rate is reduced, allowing for a potential adequate modulation of the feedback, with a probable consequent protection against this comorbidity[73].

Table III shows the efficacy of many studies which encompassed the main drugs here mentioned in relation to the placebo group and other commonly prescribed oral antidiabetics.

Drug Interaction

Another important theme to be discussed is the drug interaction between these new medications and the commonly prescribed drugs used among T2DM patients[74-78]. These individuals simultaneously use other medications associated with their risk factors. Some examples of these drugs are simvastatin and warfarin, for cardiovascular control; metformin, sulfonylureas and other anti-hyperglycemic agents; rifampin and mefenamic acid, which are prone to alter the metabolic pathways of the drugs[27,79].

Medications used in cardiovascular treatment, like digoxin, simvastatin, valsartan, hydrochlorothiazide and warfarin did not interfere with dapagliflozin, canagliflozin and empagliflozin[24,25]. Antidiabetics like metformin, pioglitazone, glimepiride and glyburide were also well tolerated, and no dose alterations for combined therapies were made necessary[26,27]. Nevertheless, the effects of rifampin, an inducer of UGT1A9 of cytochrome P450, which is responsible for the metabolization of canagliflozin and dapagliflozin, suggest alterations in the pharmacokinetic properties described so far. For canagliflozin, not only a 28% decrease in its peak concentration was detected but also a decrease of 51% in its bioavailability could be observed when patients made use of rifampin 600 mg/day[80]. Regarding dapagliflozin, the obtained results were milder. The same dose of rifampin caused a reduction of 22% in its bioavailability, and a 51% increase in this parameter due to the use of mefenamic acid, a UGT1A9 inhibitor. In spite of these alterations, the current study does not consider the results clinically relevant[28].

Conclusions

The great amount of classes of drugs currently used in the treatment of T2DM shows the importance of this syndrome and the difficulties found for its adequate control. SGLT2 inhibitors proved to be as effective as the conventional antidiabetics used for the treatment. Besides, these inhibitors also trigger complementary positive effects, such as weight loss and BP reduction.

Urogenital infections were the most frequent adverse effects observed, especially among females. The intensity ranged from mild to moderate with no further complications. Cases of ketoacidosis have recently been reported, but new studies are required to better investigate its possible consequences. No clinically relevant drug interaction with the classic drugs used for the treatment of T2DM was observed. SGLT2 inhibitors proved to be well tolerated among patients with mild to moderate hepatic and renal dysfunction, but greater attention should be paid in the event of more severe cases.

Therefore, the new drugs here discussed represent a new promising alternative, independent from the physiologic insulin secretion mechanism, for the treatment of diabetes. However, further studies on the topic should be conducted so that the long-term risks for patients, especially in those with severe dysfunctions, can be analyzed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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