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# THE DAPAGLIFLOZINE-TYPE 2 SODIUM GLUCOSE COTRANSPORTER INHIBITOR IN THE TREATMENT OF DIABETES MELLITUS TYPE 2

**Summary**: Dapagliflozine is a highly selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) , approved for the treatment of type 2 DM patients, as a monotherapy or in combination with other medications. Compared to the placebo groups whom administered dapagliflozin have a significant reduce in HbA1c: -0.58% (dapagliflozine 2.5mg), -0.77% (dapagliflozin 5mg) and -0.89% (dapagliflozin 10mg) in comparison to the placebo group (0.23%). Weight loss associated with the use of SGLT2 inhibitor is maintained during clinical studies up to 104 weeks.The use of these drugs in the population of patients with type 2 diabetes and high risk for cardiovascular disease is associated with reduction of mortality and morbidity from cardiovascular diseases. Indirectly renoprotective effect SGLT2i is achieved by decreasing renal glucose resorption and decreasing the blood glucose concentration, with the reduction in body weight and the body mass index. Genital infections are the most common side effects of dapagliflozine and should not be used in patients with bladder carcinoma and should be prescribed cautiously in people with a history of bladder cancer and unexplained hematuria.Due to good drug tolerance, easy dosing and minimal risk of the side effects, except for genitourinary infections, dapagliflozine, as well as other drugs in this group are an adequate choice in all patients with DM type 2, especially those with high cardiovascular risk.

**Key words**: dapagliflozine,SGLT2i,diabetes mellitus type2, cardiovascular risc, genitourinary infections.

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## *Introduction*

Diabetes mellitus (DM) is one of the most common chronic, non-infectious diseases, characterized by hyperglycemia and the appearance of numerous micro and macrovascular complications. In spite of the large number of patients, over 415 million adults, and different therapeutic options, only about 50% of patients are affected by optimal glycemic control, and the number of those who achieve all therapeutic goals (optimal control of glycemia, cholesterol and arterial blood pressure levels) is only 20%. (2, 3)

Ralph DeFronzo, 2010, formulates the concept of "ominous octet" that emphasizes the interaction of numerous pathophysiological processes in the occurrence of diabetes mellitus. (4) The core of the pathophysiological process is β-cell dysfunction with insulin resistance(IR) on the periphery (skeletal muscles) and increased production of glucose at the liver, increased lipolysis in the presence of obesity, but also dysfunction neurotransmitters of the central nervous system and impairment secretion of glucagone and incretine. (5, 6, 7, 8, 9, 10) The kidney has multiple relevance for maintaining glucose homeostasis. (11) The most significant effect of kidney on glucose homeostasis is carried out through its tubule level, where approximately 180l of plasma and about 180g of glucose per day are normally filtered, and in healthy people almost no glucose in the urine, everything is resuspended via sodium-glucose transporter-SGLT. (12) About 90% of glucose is reabsorbed via SGLT2, which have high capacity but low affinity, and the remaining 10% is reabsorbed by SGLT1,which have high affinity and low capacity. (13,14,15) The amount of glucose filtered through the kidneys increases linearly with increasing plasma glucose concentrations and decreases with reduced glomerular filtration. (11) Exception from this linear relationship occurs when the resorptive capacity is exceeded and when SGLT reaches its transport capacity. Tubular maximum glucose reabsorptive capacity (TmG) is about 375mg / min. (16) This is the renal threshold for glucose resorption, and occurs if glucose concentration is over 11.0 mmol / L in healthy adults. (16) In DM2 patients this threshold is higher by about 2.2 mmol / L, which in a person with normal glomerular filtrtion (GFR) and hyperglycaemia leads to an additional glucose load of 2.78-3.89 mmol/L. (11,17,18) When the plasma glucose concentration increases above 11.0 mmol / L, the percentage of the filtered glucose that is reabsorbed decreases, and the glucose concentration in the urine increases. (12)

## *SGLT2 inhibitors in focus*

Dapagliflozine is a highly selective sodium-glucose cotransporter 2 inhibitor (SGLT2i) , approved for the treatment of only type 2 DM patients, as a monotherapy or in combination with other medications. (19) By reducing the capacity for tubular

glucose resorption and decreasing renal tubular gradient for the occurrence of glucose in the urine, the use of dapagliflozine results in an increase in kidney glucose excretion in healthy volunteers and in DM patients. (20) Urinary losses of glucosis are proportional to the concentration of glucose in blood, resulting in a greater loss in people with higher serum glucose concentration. With an average daily dose of dapagliflozine, the elimination of glucose by urine increases by about 50-80 g / day, which results in a decrease in plasma glucose concentration and consequently an improvement in glycoregulation parameters.(11,21,22) Glycosuria increase begins with the first dose and is maintained during chronic treatment for at least two years. (20, 23) This mechanism is independent of the action of insulin. (24) Therefore, the risk of hypoglycaemia is minimal and there is no risk of excessive stimulation of β-cells. (25)

The positive effects of this group of drugs are explained by: reducing β-cell stress, reducing hyperinsulinemia and increasing insulin sensitivity due to calorie restriction and consequent weight loss; by increasing the concentration of "super fuel" for the tissue, especially myocardium, promoting adaptive ketogenesis.The use of SGLT2i is accompanied by a reduction in insulin secretion and a mild increase in glucagon levels. The change of this ratio, increases the utilization of lipids. Free fatty acids are metabolized to ketone bodies in response to glucagon, and taken over by the myocardium.Ketone bodies increase myocardial efficacy without increasing oxygenation, with the risk that this gentle balance can easily be disrupted in the event of starvation, fasting, pregnancy, which can cause the development of ketosis. This increase of myocardial efficacy leads to correction of oxygenation of peripheral tissues due to the increase in hematocrit, and without the increase in cardiac frequency. (26)

## *Clinical efficiency of dapagliflozine*

SGLT2 inhibitors (SGLT2i) have a mechanism of action that is completely independent of the function of Langerhans islands of the β-cells, so a combination of these medicines with all other therapeutic options is possible. (24, 27). A significant reduce in HbA1c has been observed in many studies whether the drug is administered as a mono or as combination therapy.

Ferrannini et al. showed the efficacy of dapagliflozine in monotherapy DM2. In this study, respondents (those who did not achieve adequate glyco-regulation by hygienic-dietary regimen) were randomized to four groups (placebo, dapagliflozine 2.5mg, 5mg or 10mg). Compared to the placebo groups whom administered dapagliflozin have a significant reduce in HbA1c: -0.58% (dapagliflozine 2.5mg), -0.77% (dapagliflozin 5mg) and -0.89% (dapagliflozin 10mg) in comparison to the placebo group (0.23%). For 24 weeks of study, glycemic reduction of 1.11 mmol / L and 1.39 mmol / L with dapagliflozine of 5 mg and 10 mg were observed, and this was after the first week of treatment. The effect of therapy was also better in the group of

patients with a higher HbA1c level at the beginning of the trial. (28) Similar results were presented by Bailey et al: in addition to dapagliflozine therapy, patients with a significantly higher reduction in glycemic control, also had a significant reduction in body weight. (29) A positive effect of dapagliflozine was also demonstrated in shorter studies comparing the effects of metformin, dapagliflozine and placebo. In 12 weeks of study, a significant reduction in HbA1c (-0.55% to -0.90%) was achieved in all patients with dapagliflozine, with glycemic reduction in the first week (and ranged from 0.89 mmol / L to 1, 72 mmol / L), which is dose-dependent. (30 ) At the end of 12 weeks, 59% of patients (dapagliflozine users), 54% (metformin users) achieved the optimal level of HbA1c. (30)

In addition to the undeniable effects on glycoregulation, the drugs in this group also have a significant effect on the body mass. Some DM medicines (insulin, sulphonyl urea and glitazone ) are associated with weight gain, but their prescription (pioglitazone, glimepiride) with dapaglifozine followed by weight reduction. (31, 32, 33) In early stages of therapy, this is due to loss of fluid , and subsequent weight loss is a consequence of calories loss (average 200-300kCal per day), resulting in loss of body fat, both subcutaneous fat and visceral, as verified by the use of sophisticated MRI (magnetic resonance imaging ) techniques. (34, 35) Bailey et al. report a loss of 1.5-2.1kg in patients treated with dapagliflozine 10mg after failure of metformin therapy, with or without a sulphonylurea or insulin during 24 weeks of trial duration. Similar results have been achieved in other studies. (36, 37) Body weight to stabilize after 24 weeks. (36, 38) Higher weight loss is in patients treated for more than 6 months. (38) McGovern has shown that a higher starting body mass index is associated with a higher loss of weight. (39) Weight loss associated with the use of SGLT2 inhibitor is maintained during clinical studies up to 104 weeks. (35)

Insulin resistence (IR) and hypertension often coexist.Clinical studies show that 50% of patients with hypertension have an IR or some form of the glycoregulation disorders, while as many as 80% of people with DM2 have hypertension. The effect of dapagliflozine on arterial blood pressure was tested in patients with DM with and without arterial hypertension. In well-controled studies, the mean reduction in systolic and diastolic blood pressure was 3.6 and 1.2 mmHg in hypertensive and 2.6 and 1.2 mmHg in normotensive patients, without changes in heart rate and a mild increase in patient proportions (about 2%) with episodes of orthostatic hypotension in people who used dapagliflozine. (40) The proposed mechanisms for the reduction of blood pressure are: osmotic diuresis, mild natriurese, weight reduction, increased nitric oxide release -in response to reduction of oxidative stress due to improved glycoregulation. (41, 42)

Considering that the goal of modern DM2 therapy in addition to establishing adequate glycoregulation and reducing cardiovascular risk, numerous studies have been conducted to investigate the influence of SGLT2 inhibitors in this process. EMPA-REG OUTCOME® study from 2015. showed a significant reduction in cardio-

vascular mortality and morbidity using this class of drugs, and expected announced in 2019. the results of DECLARE-TIMI 58® (Dapagliflozin Effect on CardiovascuLAR Events, DECLARE-TIMI 58), which examined the effects of dapagliflozine. The results of a large worldwide clinical study CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors, CVD-REAL) that encompassed more than 300000 patients with newly revealed DM2. The conclusion of this and the CVD-REAL Nordic study has shown that the use of these drugs in the population of patients with type 2 diabetes and high risk for cardiovascular disease is associated with reduction of mortality and morbidity from cardiovascular diseases. (43, 44) These are the main reasons why the ADA and EASD (European association for the study of diabetes, EASD) have issued recommendations to use the drugs of this group as another therapeutic line after the primary failure of metformin, especially in people at risk of cardiovascular diseases. (45)

The role of the action of dapagliflozine is also the place of the manifestation of another significant effect of dapagliflozine, which is nephroprotection. Indirectly renoprotective effect is achieved by decreasing renal glucose resorption and decreasing the blood glucose concentration, with the reduction in body weight and the body mass index. The change in renal hemodynamics reduces intraglomeric pressure and reduce renal hyperfiltration and tubular hypertrophy, while reducing the direct toxicity of glucose to the tubules.(46, 47) Reduction of renal hyperfiltration, a marker of diabetic nephropathy, was observed, but after an observation of the normotensive subjects of type 1 DM who used SGLT2 inhibitors, empagliflozine at a dose of 25 mg. (48) It is assumed that the positive effects are the result of a decrease in Na + resorption due to SGLT2 inhibition, which causes tubuloglomerular feedback (via increased delivery of sodium to macula densa and local angiotensin II increase), vasoconstriction, decreased glomerulum pressure and reversible decrease in glomerular filtration rate (GFR) of each individual nephron.(47, 49) The effect of reducing arterial pressure with decreasing arterial stiffness, decreasing vascular resistance, decreasing serum uric acid concentration, and reducing albuminuria, without potassium level disorder and modulation of neurohormonal responses, as potential factors contributing to nephroprotection. (47, 50) Lastly, it should be noted that diuresis increase may cause an increase in hematocrit, thereby better tubulointerstal oxygenation, and an increase in the production of erythropoietin by fibroblasts. (47) There is a transient increase in urinary elimination of uric acid with a delayed reduction in its serum concentration. (51)

## *Clinical safety dapagliflozine*

By adequate selection of patients, the degree of side effects of this therapy can be reduced to minium. People with DM2 have an increased risk of asymptomatic bacteriuria, urinary tract infections, and genital infections. (52) The increase this

risk is higher in females. Researchs suggest that factors such as glucosuria stimulate bacterial growth and adherence to bacteria for the epithelium, which increases the risk of infection. (52) The use of drugs, such as SGLT2 inhibitors, facilitates the development of genital infections. These side effects can be prevented by adequate perineal hygiene and antifungal therapy.

Genital infections are the most common side effects of dapagliflozine. Infections are mild or moderate and the most common expressed in the first 6 months of therapy with a low risk of relapse , with the need for prolonged therapy. (53) Patients with a positive history of earlier genital infections have a higher risk of new infection. Infections have a good response to standard antibiotic therapy and there was generally no need to exclude dapagliflozine from therapy. (51) Urinary tract infections are less common and generally mild, and respond to conventional antibiotic therapy. (53) Although the risk of developing serious infections (pyelonephritis and urosepses) are small, it is higher than in those receiving placebo. (23)

The increase in diuresis for 350-450ml does not cause nocturia. (54) The increase of diuresis may result in a transient increase in serum creatinine. Osmotic diuresis associated with SGLT2 inhibitors could be a potential cause of volume deprivation and orthostatic hypotension, but in well-controlled studies these effects were minimal (<3%). (53)

The mechanism of action of SGLT2 inhibitors suggests the possibility of bone density influence through changes in calcium and phosphate concentrations. It has been reported that SGLT2 inhibitors conditioned an increase in serum concentration of phosphate (mainly due to increased tubular resorption) and PTH (parathyroid hormone, PTH) while reducing vitamin D concentrations. (53) Overall, these changes could lead to reduced bone formation and an increase markers of bone degeneration . Earlier opinion that a higher risk of fracture in patients on dapagliflozin therapy was not confirmed by recent meta-analysis ( 30384 patients); Fracture risk was identical for all SGLT2 inhibitors, especially in patients with GFR <45 ml / min / 1.73 $m^2$. (25)

The risk of hypoglycaemia exists if these drugs are prescribed with insulin or sulphonylurea medications, but do not lead to discontinuation of the therapy. (19)

In dapagliflozine studies, in 0.17% patients bladder carcinoma was reported, towards 0.03% of those subjects who received placebo, with many of the cases occurring during the first year of dapagliflozine therapy, which reduced the likelihood of cancer being related to by exposure to this medicine.There were four cases of bladder cancer in patients receiving dapagliflozin more than a year . Although the number of cases are small, dapagliflozine should not be used in patients with bladder carcinoma and should be prescribed cautiously in people with a history of bladder cancer and unexplained hematuria. (19) The presumed mechanism of action is that high glucose concentration increases the growth of premalignant cells. (55)

Diabetic ketoacidosis (DKA) which is more common in patients with DM1 but also seen in patients with DM2 could be fatal. FAERS (FDA Adverse Event Reporting

System -FAERS) identified 73 cases with euglycemic ketoacidosis in the period March 2013-May 2015, and the FDA issued a warning about the dangers of DKA during use of SGLT2 inhibitors. Euglycemic ketoacidosis is defined as diabetic ketoacidosis without hyperglycemia. Potential triggers for DKA are infections, reduced calorie intake, alcohol use, insulin dose reduction.

Diabetic ketoacidosis were registered in patients with both types of DM. All patients with DKA needed hospitalization, permanent discontinuation of dapagliflozine with insulin dose correction and increased carbohydrate intake. (56, 57, 58)

## *Conclusion*

Dapagliflozine, a drug from the group of SGLT2 inhibitors, is effective in reducing HbA1c, as a monotherapy or in combination with other drugs. Also,it is associated with mild reduction in body weight and arterial blood pressure. Due to good drug tolerance, easy dosing and minimal risk of the side effects, except for genitourinary infections, dapagliflozine, as well as other drugs in this group are an adequate choice in all patients with DM type 2, especially those with high cardiovascular risk.

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