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EFFECTS OF SGLT2 INHIBITORS ON GLYCEMIC CONTROL AND THE REDUCTION OF CARDIOVASCULAR AND RENAL OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES: A BIBLIOGRAPHIC REVIEW

EFEITOS DOS INIBIDORES DE SGLT2 NO CONTROLE GLICÊMICO E NA REDUÇÃO DE DESFECHOS CARDIOVASCULARES E RENAIS EM PACIENTES COM DIABETES TIPO 2: UMA REVISÃO BIBLIOGRÁFICA

EFECTOS DE LOS INHIBIDORES DE SGLT2 EN EL CONTROL GLUCÉMICO Y EN LA REDUCCIÓN DE LOS RESULTADOS CARDIOVASCULARES Y RENALES EN PACIENTES CON DIABETES TIPO 2: UNA REVISIÓN BIBLIOGRAFICO

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ABSTRACT

The objective of this study was to identify the real effects of SGLT2 inhibitors and their efficacy on glycemic control and the impact of medication on the prevention of cardiovascular events and progression of diabetic kidney disease. To develop this research, a guiding question was developed: “What are the effects of SGLT2 inhibitors on glycemic control and cardiovascular and renal outcomes in patients with type 2 diabetes?”. The searches were performed in the PubMed Central (PMC) database. Four descriptors were used in combination with the Boolean term “AND”: SGLT2 inhibitors, Diabetes Mellitus Type 2, Cardiovascular Outcomes, Renal Protection. Thus, it is observed that SGLT2 inhibitors promote glycosuria, increase insulin sensitivity, in addition to reducing arterial stiffness, improving endothelial function, slowing the rate of decline in eGFR in diabetic patients, which allows us to conclude the effectiveness of their glycemic control effects, and reduction of cardiovascular and renal events in patients with type 2 diabetes mellitus.

Keywords: SGLT2 Inhibitors. Type 2 Diabetes Mellitus. Glycemic Control. Cardioprotection. Nephroprotection.

RESUMO

O objetivo deste estudo foi reconhecer os efeitos dos inibidores do SGLT2 e sua eficácia no controle glicêmico e o impacto da medicação na prevenção de eventos cardiovasculares e na progressão da doença renal diabética. Para o desenvolvimento dessa pesquisa foi elaborada uma questão norteadora: “Quais são os efeitos dos inibidores de SGLT2 no controle glicêmico e nos desfechos cardiovasculares e renais em pacientes com diabetes tipo 2?”. As buscas foram realizadas na base de dados PubMed Central (PMC). Foram utilizados 4 descritores em combinação com o termo booleano “AND”: SGLT2 inhibitors, Diabetes Mellitus Type 2, Cardiovascular Outcomes, Renal Protection. Desse modo, observa-se que os inibidores de SGLT2 promovem glicosúria, aumenta sensibilidade à

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insulina, além de reduzir a rigidez arterial, melhorar a função endotelial, lentificam a taxa de declínio da TFGe de pacientes diabéticos, o que permite concluir a eficácia de seus efeitos de controle glicêmico, e redução de eventos cardiovasculares e renais em pacientes com diabetes mellitus tipo 2.

Palavras-chave: Inibidores de SGLT2. Diabetes Mellitus Tipo 2. Controle Glicêmico. Cardioproteção. Nefroproteção.

RESUMEN

El objetivo de esta revisión bibliográfica fue reconocer los efectos reales de los inhibidores de SGLT2 y su eficacia en el control glucémico, así como el impacto del medicamento en la prevención de eventos cardiovasculares y en la progresión de la enfermedad renal diabética. Para el desarrollo de esta investigación se elaboró una pregunta orientadora: "¿Cuáles son los efectos de los inhibidores de SGLT2 en el control glucémico y en los desenlaces cardiovasculares y renales en pacientes con diabetes tipo 2?". Las búsquedas se realizaron en la base de datos PubMed Central (PMC). Se utilizaron cuatro descriptores en combinación con el término booleano "AND": **SGLT2 inhibitors, Diabetes Mellitus Type 2, Cardiovascular Outcomes, Renal Protection.** De este modo, se observa que los inhibidores de SGLT2 promueven glucosuria, aumentan la sensibilidad a la insulina, además de reducir la rigidez arterial, mejorar la función endotelial y ralentizar la tasa de disminución del FG estimado (TFGe) en pacientes diabéticos, lo que permite concluir la eficacia de sus efectos en el control glucémico y en la reducción de eventos cardiovasculares y renales en pacientes con diabetes mellitus tipo 2.

Palabras clave: Inhibidores de SGLT2. Diabetes Mellitus Tipo 2. Control Glucémico. Cardioprotección. Nefroprotección.

1 INTRODUCTION

Type 2 diabetes mellitus (DM2) is a chronic metabolic disease characterized by insulin resistance and pancreatic beta cell failure, which leads to chronic hyperglycemia. This condition, when not managed correctly, is associated with cardiovascular and renal complications.

Chronic hyperglycemia results in damage to the vasculature, leading to microvascular and macrovascular diseases. Microvascular complications are mainly diabetic retinopathy and nephropathy, while macrovascular complications are related to accelerated atherosclerosis in different areas, such as cerebrovascular atherosclerotic disease that manifests as cerebrovascular accident (CVA), coronary artery disease (CAD) and peripheral arterial disease (PAD). Other macrovascular complications are cardiac dysfunctions, including cardiomyopathy and heart failure (SPINETTI et al., 2023).

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are oral antidiabetic drugs, and were initially used to aid glycemic control in diabetic patients in order to avoid complications. This effect is due to glycosuria, from the inhibition of SGLT2, decreasing renal glucose reabsorption. However, currently, this class of antidiabetic drugs has come to be considered as pleotropic drugs, due to their beneficial results in cardiovascular diseases and chronic kidney disease (CKD). (SANTULLI et al., 2023) Evidence suggests that there is an improvement in renal and cardiovascular outcomes in patients with T2DM, especially those with previous cardiovascular events, chronic kidney disease (CKD), or HF (XU et al., 2022).

Four SGLT2 inhibitors were approved by the FDA (Food and Drug Administration), the first was Canagliflozin in 2013, followed by Empagliflozin and Dapagliflozin in 2014 and Ertugliflozin in 2017, all of which have an effect of controlling hyperglycemia and also improving cardiovascular and renal outcomes. In clinical trials involving the use of SGLT2 inhibitors in diabetic patients, adverse reactions, such as genital infections, diabetic ketoacidosis, fractures, and amputations, were shown relative to placebo. (XU et al., 2022). However, the results of the various trials of cardiovascular outcomes with these drugs showed the benefits in reducing adverse cardiovascular events by 11%, reducing the risk of cardiovascular death or hospitalization for heart failure by 23%, and reducing the progression of kidney disease by 45%. (ROWN et al., 2021).

The objective of this literature review was to evaluate the most recent findings on the effects of SGLT2 inhibitors on glycemic control, in addition to detailing their mechanism of action and their proven efficacy in the prevention of cardiovascular and renal outcomes. By

consolidating these findings, we seek to provide a comprehensive and updated view that contributes to the optimization of disease control and also reduces associated complications, thus improving the quality of life and clinical outcomes of this patient.

2 METHODOLOGY

This is a literature review that seeks to understand the effects of glucose-sodium-2 cotransporter inhibitors, and their actions in reducing hyperglycemia and reducing complications resulting from chronic hyperglycemia. For the development of this research, a guiding question was developed through the PVO (population, variable and objective) strategy: "What are the effects of SGLT2 inhibitors on glycemic control and cardiovascular and renal outcomes in patients with type 2 diabetes?".

The searches were carried out based on searches in the PubMedCentral (PMC) database. 4 descriptors were used in combination with the Boolean term "AND": SGLT2 inhibitors, Diabetes Mellitus Type 2, Cardiovascular Outcomes, Renal Protection. The search strategy used in the PMC database was: SGLT2 inhibitors AND Diabetes Mellitus Type 2, SGLTS inhibitors AND Cardiovascular Outcomes, SGLT2 inhibitors AND Renal protection. From this combination, articles were found that were later submitted to the selection criteria. The inclusion criteria were: randomized clinical trials, meta-analyses examining SGLT2 inhibitors and in patients with type 2 diabetes; articles in English, Portuguese published in the last 10 years that address the theme proposed by this research. The exclusion criteria were: studies that exclusively involve patients without diabetes; narrative reviews, case studies; and studies with no relevant clinical outcomes or very small sample sizes.

After applying the inclusion and exclusion criteria listed above, 10 articles were selected to compose the collection.

3 RESULTS AND DISCUSSIONS

The kidneys contribute to glucose homeostasis through its filtration and reabsorption. With glomerular filtration the kidney filters about 162g of glucose daily, the amount of glucose filtered increases linearly with the increase in its plasma concentration. Glucose is absorbed in the proximal renal tubules. The threshold for reabsorption is plasma glucose concentration = 8.3 mmol/L, above this value, there is glycosuria. When the plasma glucose concentration is > 13.3 mmol/L, the maximum glucose reabsorption capacity is exceeded, and therefore the

degree of glycosuria increases linearly with increasing plasma concentrations (BROWN et al., 2021).

The transport of glucose across cell membranes in the kidney depends on two families of transporters: the facilitated glucose transporters (GLUTs) and the sodium-glucose cotransporters (SGLTs). GLUTs are responsible for passive transport, whereas SGLTs do active transport across a concentration gradient. There are two forms of sodium-glucose cotransporters: SGLT1 and SGLT2. SGLT1 is found in the small intestine and segment 3 of the proximal tubule. SGLT2 is found in the luminal membranes of the epithelial cells of segment 1 and 2 of the renal proximal tubules (BROWN et al., 2021).

In individuals with T2DM, in order to avoid glycosuria, there is a compensatory upregulation of SGLT2 expression, which leads to increased glucose reabsorption (SANTULLI et al., 2023).

Thus, based on the knowledge of the role of the kidney in glucose homeostasis, sodium-glucose cotransporter 2 inhibitors were developed, which are direct inhibitors of the SGLT2 protein, which prevents glucose from binding to the cotransporters, leading to reduced reabsorption by the proximal tubules, and results in increased excretion of sodium, glucose and water in the urine. The mechanism of action of these oral hypoglycemic agents is independent of insulin secretion by pancreatic cells, so there is a low incidence of hypoglycemia in patients, which has a higher occurrence when associated with the use of sulfoniruleia or insulin therapy (DAI et al., 2023).β

4 GLYCEMIC CONTROL

Glycemic control by SGLT2 inhibitors occurs in two mechanisms. The first is due to its effects on modulating renal glucose excretion, reducing the glucose reabsorption capacity and the threshold for glycosuria, promoting a glycosuria of 60-80g/day. The second occurs due to the improvement of glucotoxicity, due to the reduction of glucose concentration secondary to glycosuria, leading to greater insulin sensitivity in peripheral tissues (adipose tissue and skeletal muscle) and improvement in the function of β cells, with an improvement in insulin secretion. (BROWN et al., 2021) Meta-analyses of HbA1c reduction with SGLT2 inhibitors in type 2 diabetes have observed reductions of 0.5-1% of the value (BAILEY; DAY; BELLARY, 2022).

Another beneficial factor in relation to the use of SGLT2 is the weight reduction of patients, in several meta-analyses it has been noted a reduction of 2-3kg in weight after 6

months of treatment. The mechanism of weight loss is associated with glycosuria, natriuresis and aquaresis, in addition, there are changes in the use of substratesm so that there is a change from glucose oxidation to increased lipolysis, fat oxidation and formation of ketone bodies. Weight loss with SGLT2 inhibitor therapy was calculated based on urinary glucose excretion of 60-80g/day, which is equivalent to a caloric loss of 240-320 calories/day (BROWN et al., 2021).

5 CARDIOPROTECTION

Patients with type 2 diabetes have an important risk factor for cardiovascular disease, conferring a two- to three-fold increased risk of coronary artery disease, including angina, myocardial infarction, stroke, and heart failure (HF) (BROWN et al., 2021). Thus, the cardioprotective effects of SGLT2 inhibitors can be attributed to: blood pressure control, increased plasma erythrocyte levels, decreased inflammation and oxidative stress, decreased uric acid, prevention of ischemia injury, and improved cardiac and vascular function (XU et al., 2022).

Studies indicate that the reduction in blood pressure by SGLT2 is due to the mechanism of volume reduction secondary to diuresis and natriuresis, in addition, other effects, such as loss of calories and decrease in fat mass, resulting from the increase in diuresis and glycosuria, also contribute to the reduction of blood pressure. The reduction in blood pressure does not accompany the increase in heart rate, which indicates that there is no activation of the sympathetic nervous system, demonstrating that this class of antidiabetics has a beneficial effect on HF patients (ZENG et al., 2021).

The efficiency of reducing arterial stiffness, it was demonstrated in an observational study the ability of SGLT2 inhibitors, especially dapaglifozin, empaglifozin and canaglifozin, to reduce PWV (pulse wave velocity), which is the main parameter of arterial stiffness. In addition, in other studies, improved endothelial function has been observed, which may be mediated by increased nitric oxide, reduced oxidative stress, or activation of voltage-gated potassium channels and protein kinase G (ZENG et al., 2021).

In addition, there is an inhibition of NHE1 and NHE3 which are sodium-hydrogen exchangers, and transfer sodium () to the cell in exchange for the export of protons. NHE1 is present in cardiomyocytes and its activation can lead to increased intracellular ions and calcium, and this effect is involved in abnormal myocardial hypertrophy and ischemia-perfusion injury. NHE3 is expressed in the proximal tubule and contributes to the tubular

reuptake of these receptors. Thus, although there is no expression of SGLT2 in the heart, SGLT2 inhibitors from NHE1 blockade can reduce intracellular concentrations of and protect the heart from intracellular overload. Similarly, they can inhibit NHE3 that improves natriuresis, restores sodium homeostasis throughout the body, and improves heart function (ZENG et al., 2021).$Na^+Na^+Ca^{2+}Na^+.Na^+Ca^{2+}Ca^{2+}$

In some studies, it has been shown to be an increase in hematocrit after treatment with SGLT2, and has been associated with increased plasma volume and increased production of erythropoietin (ZENG et al., 2021), which increases oxygen delivery to tissues, especially the kidney, reducing renal hypoxia (GIORGINO et al., 2020).

Three large clinical trials were conducted to evaluate the effects of SGLT2 inhibitors on cardiovascular outcomes, EMPA-REG, CANVAS and DECLARE-TIMI, which respectively evaluated Empaglifozin, Canaglifozin and Dapaglifozin, and showed that there is a significant reduction in cardiovascular events, especially in patients with established atherosclerotic cardiovascular diseases. Not showing as much benefit in patients who had multiple risk factors but no established cardiovascular disease. In addition, it was seen in these studies, a benefit in reducing hospitalization in heart failure, in patients with and without type 2 diabetes mellitus and both in HFrEF and HFpEF (BROWN et al., 2021).

The pathogenesis of HF involves activation of the immune system, with the Toll-Like (TLR) receptor expressed predominantly in the heart, TLR 4, is closely associated with myocardial inflammation. Thus, with its activation, there is the expression of pro-inflammatory cytokines, such as IL-6, IL-1 and TNF-α, which in the long term leads to cardiac remodeling and deterioration of function. Thus, some studies have shown that SGLT2 inhibitors have an anti-inflammatory effect by reducing the formation of pro-inflammatory cytokines. This can be explained by different signaling pathways, such as the kappa factor B (NF-κB) signaling pathway, the mitogen-activated protein kinase (MAPK) pathway, and the TLR4 pathway (ZENG et al., 2021).

Based on these findings, SGLT2 is being introduced as standard therapy for heart failure with reduced ejection fraction (HFrEF), is indicated as add-on therapy to RAAS inhibitors and beta-blockers in patients with New York Heart Association (NYHA) grades YHA II-IV in the current update of the American Board of Cardiology (ACC) consensus. Meta-analyses have described a reduction in mortality and an even greater reduction in hospitalization for HF (KOLESNIK et al., 2022).

However, in acute HF, limitations in studies such as sample size and study method have failed to determine whether SGLT2 inhibitors can be safely applied in these patients (ZENG et al., 2021).

Currently, a number of studies have researched the antiarrhythmic properties of SGLT2 inhibitors. Its effectiveness in reducing hospitalization in cases of heart failure, due to improved cardiac function, is leading to a reduction in the number of ventricular arrhythmias. In addition, from evidence in clinical trials, a lower incidence of atrial fibrillation and other atrial arrhythmias was revealed in diabetic patients treated with SGLT2 inhibitors, when compared to other glucose-lowering drugs. Despite these results, no pathways or molecular mechanisms have been identified for these antiarrhythmic properties (KOLESNIK et al., 2022).

A randomized, double-blind, placebo-controlled clinical study, the EMPA-ICD, was launched to demonstrate the antiarrhythmic effects of empagliflozin in patients with type 2 diabetes and using an implantable cardioverter defibrillator (ICD) or resynchronizer defibrillator (CRT-D), the SGLT2 inhibitor group had a significant reduction in the number of ventricular arrhythmias compared to the placebo group. These effects have been associated with increased blood ketone levels, improved myocardial energy metabolism, increased hematocrit, decreased B-type natriuretic peptide, and reduced body weight.

6 NEPHROPROTECTION

Kidney disorders are common complications in T2DM. Many people with the disease already have some degree of kidney dysfunction at the time of diagnosis, and it can evolve over time, leading to the development of chronic kidney disease and end-stage renal disease (ESRD). Some observational studies have identified the duration of diabetes as an independent risk factor for the progression of kidney failure (GIORGINO et al., 2020).

Diabetic kidney disease is recognized to be a progressive chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73, may be accompanied by micro- or macroalbuminuria, with an underlying glomerulopathy of thickened basal capillary membranes, diffuse mesangial sclerosis, and nodular sclerosis. The normal rate of age-related decline in eGFR (~1ml/min/1.73when eGFR is > 60 ml/min/1.73) is doubled in DM2 with CKD (BAILEY; DAY; BELLARY, 2022).$m^2 m^2 por\ ano\ m^2$

The action of SGLT2 in nephroprotection occurs due to numerous factors, one of them is a reduction in glomerular hyperfiltration, this occurs due to the increase in the dense

macula, through the tubuloglomerular feedcaback that stimulates the relaxation of the efferent arterioles and the constriction of the afferent arterioles. This reduces intraglomerular pressure and reduces glomerular hyperfiltration, which are critical to preserving kidney function. Thus, there is an acute reduction in the glomerular filtration rate (GFR), but it is a reversible effect (SANTULLI et al., 2023). This drop in GFR is initially about 5ml/min/1.73, reaches its lowest point in 1-2 weeks, and returns to pre-treatment values over the next 3-9 months. Evidence from long-term trials indicated that eGFR declined at a slower rate with the use of SGLT2 inhibitors than in placebo-treated patients and that albuminuria was lower (BAILEY; DAY; BELLARY, 2022).Na^+m^2

In addition, the class of antidiabetics reduces the consumption of renal oxygen, by inhibiting the reabsorption of , decreases the amount of sodium that enters the cells and therefore decreases the expenditure of ATP, by ATPase, responsible for pumping it out of the cells. This effect becomes more significant in diabetes, when hyperperfusion increases the amount of ultrafiltered knot (SANTULLI et al., 2023).Na^+ $Na^+/K^+Na^+Na^+$

In addition, other factors of these antidiabetic drugs that corroborate nephroprotection are: anti-inflammatory, anti-oxidative and antifibrotic effects. In a study in diabetic rats by Ojima et al., the effect of empaglifozin in reducing the expression of advanced glycosylation products (AGEs), receptors of advanced glycosylation products (RAGE), which results in the inhibition of oxidative stress secondary to hyperglycemia (DAI et al., 2023), was observed.

Another important factor of SGLT2 is the ability to reduce the progression of chronic kidney disease in diabetic patients, which occurs through the reduction of chronic hyperurekaemia. They act by eliminating glucose, which competes with glucose transporter protein 9 (GLUT9) present in the renal tubules and which are responsible for the reabsorption and excretion of urate. In this way, there is a reduction in urate reabsorption and an increase in uric acid excretion (DAI et al., 2023).

The increase in glycosuria secondary to the effects of SGLT2 inhibitors leads to a state of relative glucose deficiency, triggering lipolysis in adipose tissue, fatty acid oxidation, and ketone body formations. Ketone bodies are more efficient for energy production in renal tubular cells than glucose, so oxygen consumption is reduced in the presence of mild ketosis. Thus, studies suggest the use of ketone bodies as an energy substrate as a form of renoprotection (GIORGINO et al., 2020).

The nephroprotective effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus were evaluated in five large cardiovascular outcome trials: EMPA-REG OUTCOME

(empaglifozin), CANVAS and CANVAS-R (canaglifozin), DECLARE-TIMI 58 (dapaglifozin), and VERTIS CV (ertugliflozin).

In the EMPA-REG OUTCOME study, the effects of empagliflozin treatment on rates of acute renal failure and AKI were greater in patients with baseline GFR < 60 ml/min/1.73. In the CANVAS program, canaglifozin showed the ability to reduce renal outcomes constantly at different levels of baseline albuminuria, but with absolute benefits in those with macroalbuminuria. DECLARE-TIMI 58 demonstrated that dapaglifozin reduced the increase in urinary albumin-creatinine ratio (UACR), which is an important indicator of kidney disease progression, especially in patients with T2DM (GIORGINO et al., 2020).m^2

These studies have proven the efficacy of SGLT2 inhibitors in the treatment of patients with type 2 DM and mild to moderate renal impairment (eGFR >30 ml/min/1.73). However, efficacy and safety in patients with stage G4 and G5 diabetic kidney disease remained uncertain until the release of the results of the DAPA-CKD and EMPA-KIDNEY studies. m^2

In the DAPA-CKD study, it was evidenced that the use of dapaglifozin is effective in reducing the risk of sustained decline in eGFR> 50%, CKD and death from kidney disease, there was also a significant reduction in proteinuria. In EMPA-KIDNEY showed that groups that were treated with empaglifozin reduced risks of cardiovascular and renal events, hospitalization, and progression of kidney disease in patients with chronic diabetic disease and stage 4 CKD (DAI et al., 2023).

Furthermore, the CREDENCE study, which was limited to patients with diabetic kidney disease (DKD), highlighted that canaglifozin was effective in reducing cardiovascular and renal events, as well as showing results in delaying the progression of kidney disease in patients with DKD, including stage 4 (DAI et al., 2023).

7 CONCLUSION

It is concluded that the use of SGLT2 inhibitors in patients with type 2 diabetes mellitus, in addition to their hypoglycemic effects, has benefits in reducing the risk of cardiovascular and renal complications. SGLT2 are effective in reducing renal glucose reabsorption, leading to glycosuria and, consequently, improved insulin sensitivity and glycemic control. In addition, its ability to reduce blood pressure and weight loss secondary to glycosuria, promote a better quality of life for patients.

Cardioprotection is related to multifactorial mechanisms, resulting from the effects of SGLT2, such as the reduction of arterial stiffness and the improvement of endothelial function,

which reduce the risk of cardiovascular death, atherosclerotic events, hospitalization for heart failure, and antiarrhythmic properties. Regarding renal function, antidiabetic drugs have demonstrated a favorable impact on the progression of chronic kidney disease, with evidence of a slower decline in the eGFR rate of diabetic patients and also on the reduction of albuminuria, being considered an excellent therapeutic option in patients with mild to moderate renal impairment, delaying the need for renal replacement therapy.

In addition, recent studies have shown that medications such as empaglifozin, dapaglifozin, and canaglifozin have been found to be effective options for patients with advanced stage chronic kidney disease (stages 4 and 5).

Thus, SGLT2 inhibitors are fundamental in the management of patients with type 2 diabetes, who are at increased risk for cardiovascular events and chronic kidney disease. The results of the studies reinforce the need to incorporate these drugs into the treatment of these patients, for better survival and reduced risk of complications.

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