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IMPACT OF SGLT2 INHIBITORS ON HEART FAILURE

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Abstract: Heart failure (HF) affects up to more than 20% of patients with type 2 diabetes (DM2), even more in the elderly. Finally, the updated clinical evidence of the benefits of SGLT2i in HF was summarized. Thus, this review aimed to analyze the cardioprotective mechanisms of glucose transporter sodium 2 inhibitors (SGLT2i) in patients with HF, as well as their clinical impact on cardiovascular events. to intracellular sodium-reducing molecules. This provides its consequent cardioprotective effect, which justifies its significant reduction in CV events, especially in higher-risk populations.
Keywords: SGLT2 inhibitors, heart failure, pathophysiology, type 2 diabetes, cardiovascular risk.

INTRODUCTION

In recent years, large randomized controlled trials have demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors improve cardiovascular outcomes independent of diabetes, including risk of heart failure hospitalization (CHF), cardiovascular death, and all-cause mortality. As a hypoglycemic drug, SGLT2 inhibitors have been shown to play a significant role in reducing major adverse cardiovascular outcomes and hospitalization for heart failure initially in patients with diabetes. The magnitude of its impact was subsequently shown to be potentially independent of – or at least separate from – its glucose-lowering value with some hypotheses behind the exact mechanisms of its actions. The rapid accumulation of such evidence showing its favorable impact has triggered new research exploring its potential in cardiovascular outcomes and mortality in larger cohorts, not necessarily limited to diabetic populations. In response to this, two large randomized controlled trials investigated the impact of SGLT2 inhibitors in patients with heart

failure, the cohort being composed of patients with and without diabetes.

With an increasing number of trials reporting SGLT2 inhibitors in patients with and without diabetes, the aim of this non-systematic review is to provide a concise assessment of all available evidence to date and to analyze data from existing studies that focus on patients with heart failure. , to better understand the clinical implications of using SGLT2 inhibitors.

EPIDEMIOLOGY OF HEART FAILURE IN TYPE 2 DIABETES

Type 2 diabetes mellitus (DM2) is a systemic, complex and chronic disease. Its prevalence has been growing in recent decades, mainly due to the increase in obesity and sedentary lifestyle. T2DM is burdened by an elevated risk for several cardiovascular diseases (CVD), with heart failure (HF) a more common initial presentation than myocardial infarction (MI). The estimated prevalence of HF in patients with DM2 varies from 9 to 22%, being even higher in those aged ≥60 years. The risk of HF in patients with T2DM, almost double that of the general population, is affected by several risk factors.]. Particularly, longer disease duration, obesity, hypertension, coronary artery disease (CAD), peripheral artery disease (PAD), nephropathy, retinopathy and higher NT-proBNP increase the risk of HF in T2DM. Furthermore, in the Framingham study, a gender difference was reported, with risk five times and 2.4 times higher in diabetic women and men, respectively. Patients with HF are often insulin resistant, which can, in turn, increase the onset of diabetes or make it worse. Indeed, several large cohort studies have reported an incidence of diabetes in patients affected by HF varying between 30% and 50%, also suggesting a mutual relationship between these two diseases. HF and DM2, when coexisting, are associated with a worse outcome of morbidity and mortality, and DM2 is also a predictor of symptomatic HF.

Thus, the objective of this review is to evaluate the cardioprotective role of glucose transporter sodium 2 inhibitors (SGLT2i) in patients affected by both conditions.

PATHOPHYSIOLOGY OF HEART FAILURE IN TYPE 2 DIABETES

T2DM has multiple mechanisms contributing to the development of myocardial dysfunction, which affect cardiac relaxation, contractility and compliance. Structural heart disease in T2DM can develop from either myocardial ischemia or infarction, mainly due to increased atherosclerosis, atherogenic dyslipidemia, and endothelial dysfunction. All of these can, in turn, lead to thrombosis, inflammation and vulnerable coronary plaque. Diabetic cardiomyopathy, in fact, is defined as the presence of diastolic or systolic cardiac dysfunction in patients with diabetes in the absence of other causes of cardiomyopathies. The term was first coined in 1972 by Rudler et al. after post-mortem evidence of cardiomegaly in the absence of major CAD in T2DM patients.

Cardiac and non-cardiac complications of DM2 have been related to oxidative stress, increased in DM2 and mainly due to various abnormalities (eg, hyperglycemia, inflammation, and dyslipidemia). As a consequence, an increase in the production of leptin, a promoter of myocardial inflammation, triggers an impairment in the regulation of paracrine adipokines. Furthermore, the inflammatory state also increases oxidative stress, increasing leukocyte migration and inducing the production of endothelial reactive oxygen species (ROS) through the activation of nicotinamide adenine dinucleotide phosphate oxidase, thus affecting the coronary microvascular. A high level of ROS occurs in autophagy, apoptosis or

necrosis of cardiomyocytes and is capable of decreasing the bioavailability of NO due to the shift of NO to peroxynitrite by the superoxide anion, which leads to vasodilator impairment. Consequently, left ventricular diastolic dysfunction is facilitated. Inflammation has also been implicated in a newly recognized pathological process called endothelial-mesenchymal transition (endoMT). It appears that both TGF-β and Slug signaling pathways are implicated in the displacement of endoMT endothelial cells towards mesenchymal cells, leading to fibrosis and ventricular remodeling.

Therefore, in addition to the wear and tear and reduction of global cardiac function, DM2, and especially hyperglycemia and the IR-induced pro-inflammatory state, seem to trigger several mechanisms impaired, resulting in changes in cardiomyocyte calcium handling, reduced cardiac contractility and relaxation. The inflammatory signal has also been suggested as a key pathophysiological mechanism of dysfunction. myocardial infarction, as also suggested in HF of other etiologies, and is mainly upregulated due to epicardial fat hypertrophy.

METABOLIC MECHANISMS

A healthy heart needs a large amount of energy to maintain normal contractile function as it consumes various substrates including glucose and FFA, with over 95% ATP provided by mitochondrial oxidative phosphorylation and, to a lesser extent, by glycolysis. Under stressful conditions (eg, HF and/or DM2), the glucose used by the heart muscle is compromised, thus entrusting most of the metabolism to the consumption of FFA, which is less efficient due to the increased demand for oxygen by the myocardium. In addition, lipotoxicity may occur due to increased production of reactive oxygen species (ROS) and impaired absorption of calcium from the reticulum.sarcoplasmatic, with the subsequent development of diastolic dysfunction.

Ketone bodies represent a good alternative substrate, capable of improving cardiac metabolic efficiency. Some studies in humans and animal models have shown improvement in cardiac function and metabolism by beta-hydroxybutyrate (β-OHB), thus inducing reverse ventricular remodeling, with consequent improvement in cardiac output and diastolic function. In addition, ketone bodies also exert an anti-inflammatory role by suppressing activation of P3 receptor inflammasome (NLRP3) activity, similar to the nucleotide oligomerization domain.

HEMODYNAMIC PROTECTION MECHANISMS

Obesity and T2DM can also lead to HFpEF, induced by increased cardiac preload, which develops due to volume overload in response to plasma volume expansion. In these patients, IR and proinflammatory cytokines released by hypertrophic visceral adipocytes cause arterial stiffness, endothelial dysfunction in arterioles, and reduced capillary density at the systemic and heart levels, thus increasing cardiac afterload. The direct cardiac effects of SGLT2i include an improvement in both preload, secondary to natriuresis and osmotic diuresis, and afterload, secondary to a reduction in sodium and circulating volume, through a reduction in systolic and diastolic blood pressure (3- 5 mmHg and 2 to 3 mmHg, respectively), without any increase in heart rate and reducing arterial stiffness.

Several mechanisms seem to be involved in the reduction of blood pressure (BP) induced by SGLT2i, such as the reduction of sodium reabsorption in the proximal renal tubule with a consequent increase in diuresis, the improvement of vascular function in terms of stiffness and vascular resistance, and body weight reduction.

ANTI-EFFECTS ON AUTOPHAGY AND STRESS

Autophagy is the process by which the balance of cellular homeostasis is maintained after elimination of potentially harmful substances and recycling of cellular components as an adaptive response to metabolic stress, including hypoxia. Autophagy induction pathways involve activation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and hypoxia-inducible factors (HIF-1alpha and HIF-2alpha). Based on experimental studies, SGLT2i can activate all these pathways, and the interaction of all these mediators can stimulate autophagy. This lysosome-mediated degradation pathway is responsible for the clearance of damaged organelles and, consequently, for reducing inflammasome activation and mitigating cardiomyocyte dysfunction and coronary microvascular injury.

CARDIOPROTECTIVE MECHANISMS OF SGLT2 INHIBITORS

SGLT2i, also known as gliflozins, represents an effective and innovative treatment option for patients with T2DM. This class of drugs, in addition to simple glycemic control, has also been shown to be effective in the management of complications related to DM2 in the medium and long term. SGLT2i also demonstrated a significant reduction in atherosclerosis-related events, HF hospitalizations, and cardiovascular and all-cause mortality, achieved by several mechanisms discussed below. Cardiovascular Benefits of SGLT2i: Clinical Outcomes and Impact on MACEs.

The 2019 guidelines on diabetes, pre-diabetes and cardiovascular disease from the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) recommend the use of SGLT2i in patients with T2DM and CVD or, at a very high/high cardiovascular (CV) risk, to reduce CV events (class I, level A). The impacts of long-established oral glucose-lowering drugs on cardiovascular outcomes have not been evaluated in large randomized controlled trials. On the other hand, increasing evidence from randomized trials and observational studiesshow that treatment with SGLT2i reduces the risk of serious cardiovascular complications and death in patients at risk for major adverse cardiac events (MACE). Four major CV outcome studies were recently completed: EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and VERTIS-CV.

These studies showed a clear decrease in HF hospitalizations in patients treated with SGLT2. This effect was observed in patients with and without preexisting HF and in those with and without preexisting CVD. A reduction in all-cause and CV mortality was also observed, particularly significant in the EMPA-REG and CANVAS studies, but not in the DECLARE-TIMI.

A recent meta-analysis supported the conclusion that SGLT2i are effective in reducing the risk of hospitalization for HF in a large population of individuals with diabetes, regardless of prior history of CVD. However, the reduction in MACE incidence is moderate and limited to patients with established atherosclerotic CVD.

It is important to note that the antiproteinuric effect of SGLT2i is extremely evident in all RCTs. This mechanism could justify the reduction of CV and renal risk in DM2. Indeed, the impact of proteinuria modification on cardiorenal risk has been documented by recent real-life studies.

FINAL CONSIDERATIONS

Several potential mechanisms may explain the ability of SGLT2i to decrease CV risk and, particularly, hospitalization for HF in patients with or without T2DM. Its effect seems to go beyond simple hyperglycemic control, as it has not been observed in other antidiabetic drugs with more significant hypoglycemic effects. The beneficial effects seem attributable to the significant reduction in intracellular sodium levels, which is well known to play a cardioprotective role in preventing oxidative stress and consequent death of cardiomyocytes. From a molecular point of view, exposure of patients to treatment with gliflozin mimics nutrient and oxygen deprivation, with consequent stimulation of autophagy. This allows maintaining cellular homeostasis through different degradative pathways. Thus, since its introduction into clinical practice, the hypothesis about the mechanisms of action of SGLT2i has changed: from simple glucosuric drugs with consequent glucose reduction, increased erythropoiesis and stimulation of ketogenesis to intracellular sodium-reducing molecules. These mechanisms of action result in a significant reduction in CV events.

Based on clinical evidence, the use of SGLT2i seems crucial in clinical practice, especially in the treatment of patients with HF. An early use of SGLT2i could have a considerable impact on prognosis in a real-life setting. Therefore, in our opinion, SGLT2i ,ust be introduced in the first stage of treatment, regardless of concomitant medications. Indeed, in several trials, they have been shown to be effective irrespective of background medication and current step-by-step HF treatment, which often produces time dilation, affecting prognosis. In the near future, we envision that SGLT2i could be used as a first-line therapy, potentially representing a cornerstone to build HF therapy.

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