Impactos dos inibidores de SGLT2 na insuficiência cardíaca com fração de ejeção reduzida em diabéticos

Impact of SGLT2 Inhibitors on Heart Failure With Reduced Ejection Fraction in Diabetics

Impacto de los inhibidores de SGLT2 en la insuficiencia cardíaca con fracción de eyección reducida en diabéticos

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RESUMO

Objetivo: A insuficiência cardíaca com fração de ejeção reduzida (ICFER) e o Diabetes Mellitus tipo 2 (DM2) são condições crônicas frequentemente associadas, resultando em um prognóstico desfavorável e elevada mortalidade cardiovascular. Esta revisão sistemática tem como objetivo avaliar o impacto dos inibidores do cotransportador de sódio-glicose 2 (iSGLT2) na ICFER em pacientes com DM2. A pesquisa foi conduzida na base de dados PubMed, abrangendo o período de 2020 a 2025, e seguiu a estratégia PICO para a seleção de ensaios clínicos, meta-análises e revisões sistemáticas. Os resultados dos estudos analisados, incluindo ensaios com Dapagliflozina, Empagliflozina e Canagliflozina, demonstraram consistentemente que os iSGLT2 reduzem significativamente o desfecho combinado de morte cardiovascular e hospitalizações por insuficiência cardíaca. Além dos benefícios cardiovasculares, observou-se melhora no controle glicêmico e um perfil de segurança favorável. A presente revisão reafirma o papel fundamental dos iSGLT2 como uma terapia essencial no manejo de pacientes com ICFER e DM2, modificando positivamente o curso da doença e melhorando a sobrevida e qualidade de vida.

Palavras-chave: Inibidores de SGLT2 1; Insuficiência Cardíaca com Fração de Ejeção Reduzida 2; Diabetes Mellitus tipo 2 3.

ABSTRACT

Objective: Heart failure with reduced ejection fraction (HFrEF) and type 2 Diabetes Mellitus (DM2) are frequently associated chronic conditions, resulting in an unfavorable prognosis and high cardiovascular mortality. This systematic review aims to evaluate the impact of sodium-glucose cotransporter 2 (iSGLT2) inhibitors on HFrEF in patients with DM2. The research was conducted in the PubMed database, covering the period from 2020 to 2025, and followed the PICO strategy for the selection of clinical trials, meta-analyses and systematic reviews. The results of the studies analyzed, including trials with Dapagliflozin, Empagliflozin and Canagliflozin, consistently demonstrated that iSGLT2 significantly reduces the combined outcome of cardiovascular death and hospitalizations for heart failure. In addition to the cardiovascular benefits, improvement in glycemic control and a favorable safety profile were observed. The present review reaffirms the fundamental role of iSGLT2 as an essential therapy in the management of patients with HFrEF and DM2, positively modifying the course of the disease and improving survival and quality of life.

Keywords: SGLT2 inhibitors 1; Heart Failure with Reduced Ejection Fraction 2; Type 2 Diabetes Mellitus 3.

RESUMEN

Objetivo: La insuficiencia cardíaca con fracción de eyección reducida (ICFER) y la diabetes mellitus tipo 2 (DM2) son enfermedades crónicas frecuentemente asociadas, lo que resulta en un pronóstico desfavorable y una alta mortalidad cardiovascular. Esta revisión sistemática tiene como objetivo evaluar el impacto de los inhibidores del cotransportador de sodio-glucosa 2 (iSGLT2) sobre la HFrEF en pacientes con DM2. La investigación se realizó en la base de datos PubMed, abarcó el período de 2020 a 2025, y siguió la estrategia PICO para la selección de ensayos clínicos, metanálisis y revisiones sistemáticas. Los resultados de los estudios analizados, incluidos los ensayos con Dapagliflozina, Empagliflozina y Canagliflozina, demostraron consistentemente que iSGLT2 reduce significativamente el resultado combinado de muerte cardiovascular y hospitalizaciones por insuficiencia cardíaca. Además de los beneficios cardiovasculares, se observó una mejora en el control glucémico y un perfil de seguridad favorable. La presente revisión reafirma el papel fundamental de iSGLT2 como terapia esencial en el manejo de pacientes con ICFEr y DM2, modificando positivamente el curso de la enfermedad y mejorando la supervivencia y la calidad de vida.

Palabras clave: Inhibidores de SGLT2 1; Insuficiencia cardíaca con fracción de eyección reducida 2; Diabetes mellitus tipo 2 3.

REVISÃO

Introduction

Heart failure (HF) is characterized by symptoms such as dyspnea, lower limb edema, and fatigue. It is a complex and progressive clinical syndrome due to the heart's inability to pump blood effectively, resulting in reduced cardiac output, which impairs the body's metabolic functions. HF is related to left ventricular ejection fraction (LVEF) and is categorized into three types: HF with preserved ejection fraction (HFpEF), with an LVEF ≥50%; intermediate or mildly reduced ejection fraction (HFmrEF), with an LVEF between 40% and 49%; and reduced ejection fraction (HFrEF), with an LVEF ≤40%. HFrEF is one of the most challenging forms of the disease, accounting for approximately 50% of HF cases and often coexisting with other diseases, such as diabetes mellitus (DM), especially type 2 DM, which worsen its prognosis[1,2].

Type 2 DM is one of the most prevalent and impactful comorbidities in patients with HFrEF, establishing a complex relationship. DM not only increases the risk of developing HF but also worsens disease progression, worsening the prognosis of patients diagnosed with HF. Studies indicate that more than 70% of patients with T2DM die due to cardiac complications, which represents a significant public health concern[3].

In the last few years, cotransporter 2 inhibitors (SGLT2i) has emerged as novel hypoglycemic agents with favorable outcomes for cardiovascular and renal events. Such results include a significant reduction in hospitalizations for HF in patients with T2DM, as well as a reduction in cardiovascular (CV) mortality in patients with HFrEF. This benefit is evidenced by the mechanism of action of this drug, which inhibits the SGLT2 transporter in the proximal renal tubule, resulting in glycosuria (i.e., osmotic diuresis), reducing plasma volume, which directly contributes to the reduction of cardiac preload and afterload. Therefore, in-depth studies on this topic are imperative to improve the prognosis of patients with these syndromes[3].

Objective

This article aims to evaluate the impact of SGLT2 inhibitors on heart failure with reduced ejection fraction in patients with type 2 Diabetes Mellitus.

Methodology

The study consists of an integrate literature review, the research was conducted in the PubMed database , covering the period of the last five years (2020-2025).

Initially, the PICO strategy was used to define the research question: what are the impacts of SGLT2 inhibitors on heart failure with reduced ejection fraction in patients with type 2 diabetes mellitus? With this method, we considered "P" as patients with heart failure with reduced ejection fraction and type 2 diabetes; "I" as studies evaluating SGLT2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin); "C" as studies with a comparator, with placebo; "O" as studies with a

reduction in cardiovascular mortality, hospitalization for HF, and improvement in glycemic assessment.

The inclusion criteria were: articles published in the last five years, available in Portuguese or English, free full text, clinical trials, meta-analyses, and systematic reviews. Furthermore, we excluded studies with biases of interest; studies without complete data, letters to the editor, opinion pieces, and case studies.

Data extraction was carried out in September 2025, using descriptors and corresponding terms, verified from the Health Sciences Descriptors (DeCs) and Medical Subject platforms. Headings (MeSH), namely: "SGLT2 Inhibitors", "Heart Failure with Reduced Ejection Fraction", and "Type 2 Diabetes Mellitus". The search yielded 123 articles. Initially, 32 articles were selected based on their titles and abstracts, using the inclusion and exclusion criteria mentioned above. After this stage, each paper was read, and those that did not fit the topic of this review were disqualified, resulting in a total of 12 articles selected for this review.

Results

SGLT2 inhibitors have shown numerous cardiovascular benefits, particularly in patients with T2DM, according to the results of various studies. Overall, SGLT2 inhibitors reduced hospitalizations for HF and cardiovascular mortality in patients with HFrEF, in addition to demonstrating good tolerability of adverse effects. They also consistently reduced glycated hemoglobin (HBA1c) levels and body weight, improving survival in patients with T2DM[3].

In the dapagliflozin study, 6,263 patients were randomly assigned to receive dapagliflozin or placebo, which demonstrated a reduction in the number of cardiovascular deaths and heart failure events in the dapagliflozin group compared to the placebo group. Furthermore, another study with dapagliflozin evaluated patients aged >18 years and LVEF <40%, including 17,160 patients aged >40 years with T2DM. Of these, 1,724 patients had a history of HF. The results showed a significant reduction in the risk of CV death in patients with T2DM and improvement in HF symptoms. Overall, dapagliflozin was well tolerated, demonstrating a safety profile in patients with HF. However, despite its tolerability, its mechanism of action can cause volume depletion, leading to hypotension, and when associated with insulin, it can increase the risk of hypoglycemia[4,5].

Empagliflozin was evaluated in a randomized study comparing its effects with placebo in 3,730 patients with HFrEF, whether or not coexisting with T2DM. Patients received either 10 mg of empagliflozin or placebo daily. The study showed promising results regarding the reduction in the risk of CV death or hospitalization for HF in the empagliflozin group. Furthermore, a significant reduction in HbA1c was observed in patients with higher blood glucose levels treated with empagliflozin[6,7].

Canagliflozin was studied in patients with DM2 and HFrEF, which showed a reduction in the risk of CV events, in addition to considerably reducing HbA1c in patients with high blood glucose, more effectively preventing cardiovascular effects than treatment based on glycated hemoglobin[7].

Discussion

Type 2 diabetes mellitus is characterized as a metabolic disorder with an increasing prevalence associated with obesity. The pathophysiology of T2DM is known to be related to insulin resistance and a gradual decrease in the pancreas' ability to release insulin-producing beta cells. Thus, hyperglycemia is common, negatively impacting metabolism. The disease presents with micro- and macrovascular complications, with CVD, especially HF, having the greatest impact on mortality in the diabetic population[7].

Thus, with the development of drugs considered antidiabetic, several pharmacological options could be incorporated into existing treatments, or even in isolation, enabling a greater protective effect for patients, since their functions are also considered cardioprotective, that is, the results go beyond the reduction of blood glucose for patients with DM2, namely, iSGLT2[8].

SGLT2 inhibitors act by reducing renal glucose reabsorption and, consequently, increasing its urinary excretion, controlling blood glucose levels in patients with T2DM. This occurs because these medications inhibit the SGLT2 transporter, which is expressed in the renal tubules and is responsible for glucose reabsorption by the kidneys. SGLT2 inhibitors are present in the therapeutic forms of empagliflozin, dapagliflozin, and canagliflozin, which, as seen previously in this study, have demonstrated potent cardioprotective effects in addition to their benefits against T2DM[7,8].

It is known that umerous treatment guidelines for HF exist, and SGLT2-i therapy, particularly dapagliflozin and empagliflozin, has recently been incorporated into these guidelines for patients with HFrEF. These patients underwent placebo-controlled clinical trials, such as DAPA-HF and EMPEROR-Reduced, which evaluated the efficacy and safety of SGLT2-i therapy. The results showed a 26% reduction in hospitalization or CV death with dapagliflozin versus placebo, and a 25% reduction in CV death with empagliflozin[9].

Furthermore, despite their beneficial effects, the mechanism of action of SGLT2 inhibitors in cardiovascular disease remains mysterious. There are hypotheses that these drugs alter myocardial fuel consumption, demonstrating increased fatty acid oxidation and increased ketone body consumption. Furthermore, studies have found that empagliflozin is associated with increased mitochondrial calcium, which influences ATP activation during cardiac muscle contraction. Therefore, SGLT2 inhibitors increase the heart's energy output, improving its contractile capacity[10,11].

It was observed in a study with canaglifozin a significant reduction in serum insulin concentrations and HOMA- IR, which was associated with an improvement in NYHA class. These findings suggest that canagliflozin contributed to reducing insulin overload, which resulted in clinical benefits for patients with HF. This finding demonstrates that hyperinsulinemia increases the expression of cardiac and renal sodium-hydrogen exchanger isoforms, leading to cardiac dysfunction and is considered one of the main causes associated with the development of HF in T2DM. This suggests that treatment with SGLT2 inhibitors positively impacted the clinical manifestations of HF by correcting hyperinsulinemia and insulin resistance[11].

Final Considerations

The present study confirms the role of sodium-glucose cotransporter 2 inhibitors in the treatment of heart failure with reduced ejection fraction in patients with type 2 diabetes mellitus. The findings presented consistently demonstrated that these drugs significantly reduce cardiovascular mortality, as well as hospitalizations due to HF complications, improving patient survival, in addition to glycemic control.

The favorable safety profile and good tolerability, despite potential adverse events, reinforce the positive risk-benefit ratio. In summary, SGLT2i stand out for their efficacy in improving cardiovascular hemodynamics, representing a significant advance, enhancing a new management strategy and clinical outcomes for patients with HFrEF and T2DM.

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