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Editorial Board Member of *World Journal of Cardiology*, Akshyaya Pradhan, MD, DM, FACC, FSCAI, FESC, FAPSIC, Professor (Jr), Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh 226003, India. akshyaya33@gmail.com

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LETTER TO THE EDITOR

Effectiveness and mechanisms of sodium-dependent glucose transporter 2 inhibitors in type 2 diabetes and heart failure patients

Yan-Xi Zhang, Hai-Sheng Hu, Bao-Qing Sun

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Yan-Xi Zhang, Hai-Sheng Hu, Bao-Qing Sun, Department of Clinical Laboratory, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Guangzhou 510120, Guangdong Province, China

Co-first authors: Yan-Xi Zhang and Hai-Sheng Hu.

Corresponding author: Bao-Qing Sun, PhD, Professor, Department of Clinical Laboratory, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease, National Center for Respiratory Medicine, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, No. 28 Qiaozhong Middle Road, Guangzhou 510120, Guangdong Province, China. sunbaoqing@vip.163.com

Abstract

We comment on an article by Grubić Rotkvić *et al* published in the recent issue of the *World Journal of Cardiology*. We specifically focused on possible factors affecting the therapeutic effectiveness of sodium-dependent glucose transporter inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM) and their impact on comorbidities. SGLT2i inhibits SGLT2 in the proximal tubules of the kidneys, lowering blood glucose levels by inhibiting glucose reabsorption by the kidneys and causing excess glucose to be excreted in the urine. Previous studies have demonstrated a role of SGLT2i in cardiovascular function in patients with diabetes who take metformin but still have poor glycemic control. In addition, SGLT2i has been shown to be effective in anti-apoptosis, weight loss, and cardiovascular protection. Accordingly, it is feasible to treat patients with T2DM with cardiovascular or renal diseases using SGLT2i.

Key Words: Sodium-dependent glucose transporter inhibitors; Type 2 diabetes mellitus; Heart failure; Treatment; Cardiovascular disease

Core Tip: Studies have revealed that type 2 diabetes mellitus (T2DM) patients often suffer from multiple comorbidities that can be effectively treated with sodium-dependent glucose transporter inhibitors (SGLT2i), which has been linked to their anti-apoptotic properties, promotion of weight loss, and cardiovascular protection. Correctly avoiding the risks of SGLT2i use and aggressive use of the drug in patients with T2DM and its complications to alleviate symptoms are feasible.

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TO THE EDITOR

Type 2 diabetes mellitus (T2DM), which is characterized by hyperglycemia, is a growing health problem worldwide[1,2]. More than 90% of people with diabetes have T2DM[3]. Heart failure (HF) is a complex chronic disease caused by impaired heart function[4]. HF increases the risk of cardiovascular, renal, and neurological complications by having T2DM[3]. As one of the most common cardiovascular complications, HF has a prevalence of 10% to 23% in patients with T2DM[5]. One study suggested that the pathophysiologic mechanism of HF in diabetes mellitus may be due to coexisting coronary artery disease, hypertension, or diabetes mellitus, which directly affects the structure and function of the heart [6,7]. Sodium-dependent glucose transporter inhibitors (SGLT2i), a new class of antidiabetic drugs, have recently been found to promote significant cardiovascular benefits in patients with diabetes or HF[8]. We have previously commented on the role of SGLT2i in cardiovascular function in patients with diabetes who take metformin but still have poor glycemic control[9]. This finding underscores the importance of SGLT2i as an effective treatment for patients with T2DM and asymptomatic HF.

INFLUENCING FACTORS AND POSSIBLE MECHANISMS OF SGLT2I TREATMENT EFFECTIVENESS

SGLT2i has many benefits in terms of treatment of patients with T2DM and combined HF. This has been explored by many researchers in order to identify why SGLT2i is effective. SGLT2 is the major transporter responsible for the reabsorption of glucose from the glomerular filtrate back into circulation. SGLT2i lower the renal reabsorption of filtered glucose and increase urinary glucose excretion, thereby lowering blood glucose levels[10]. Diabetes induces multiple molecular pathways in tissues. Evidence suggests that diabetes induces different forms of cellular damage; hyperglycemia-dependent oxidative stress leads to apoptosis, SGLT2i acts as an anti-apoptotic agent by lowering blood glucose levels, and inhibition of oxidative stress in diabetes ameliorates apoptosis[11]. Brown *et al*[12] suggested that obesity plays a key role in the development and progression of T2DM, and that the pathophysiology of T2DM is mediated by ectopic fat deposition. Therefore, weight loss has clear health benefits in patients with T2DM. Vallon *et al*[13] suggested that the mechanism by which SGLT2i reduces body weight is initially due to diuretic effects, whereas subsequently, this is due to an increase in lipolysis and fatty acid oxidation by shifting the substrate utilized from carbohydrates to lipids, resulting in a reduction in body fat, including visceral and subcutaneous fat. Multiple randomized trials have shown that SGLT2i effectively improves glycemic control in patients with T2DM, accompanied by a higher incidence of glycemic decline and weight loss. Research by Strojek *et al*[14] suggested that a 5.00 mg SGLT2i group lost 0.84 kg more than a placebo group, and this result was even more significant in a 10 mg SGLT2i group. Meanwhile, fasting blood glucose values were significantly decreased in a dapagliflozin-administered group, with a decrease of 0.82 mmol/L in a 2.50 mg (-0.93 mmol/L) group compared to a placebo group (-0.11 mmol/L), a result that was even more pronounced with an increased dosage of dapagliflozin[14]. Another randomized trial showed a mean total weight reduction of 1.61 kg in a 10.00 mg dapagliflozin group, compared with an increase of 0.43 kg in a placebo group[15]. A meta-analysis suggested that SGLT2i significantly reduces body weight and body mass index in patients with T2DM, with a mean difference in body weight of -2.73 kg and -1.13 kg/m^2[16]. In a study conducted in Japan, SGLT2i improved glycaemic control and reduced body weight in older adults with T2DM, resulting in a change in glycated hemoglobin A1C of -0.57% without affecting subjects' muscle mass[17].

In terms of cardiovascular protection, one study showed that SGLT2i reduced cardiac preload and afterload through osmotic diuresis[18]. This study concluded that SGLT2i-induced osmotic diuresis led to greater electrolyte-free water clearance, thereby relieving congestion and reducing cardiac preload. Osmotic diuresis lowers blood pressure, increases urinary sodium excretion, improves cardiovascular function, and reduces cardiac afterload. Na/H exchange (NHE) activity is low in normal healthy myocardium and high in HF myocardium, and a recent study found that empagliflozin could protect the heart in HF by mitigating cardiac hypertrophy through the inhibition of RSK-NHE1-mediated pathways [19]. Therefore, SGLT2i may be effective in the treatment of patients with T2DM complicated by HF.

TEARTMENT OF T2DM WITH CARDIOVASCULAR OR RENAL DISEASE WITH SGLT2i IS FEASIBLE

The use of SGLT2i is feasible for treating patients with T2DM because of its multiple protective mechanisms. This study showed a reduction in afterload in patients with T2DM after the use of SGLT2i[9]. Treatment with SGLT2i leads to better prognosis in T2DM patients with asymptomatic HF. In addition, SGLT2i has shown significant cardiorenal benefits in many studies. A meta-analysis suggested that the treatment of T2DM patients with SGLT2i results in significant reductions in systolic and diastolic blood pressures (by approximately 4.3 mmHg and 2.3 mmHg, respectively)[20]. A study based on data from the Asia Pacific, Middle East, and North America suggests that SGLT2i significantly reduces the risk of All-Cause Death, HF, myocardial infarction, and stroke[21]. A 2019 study showed a 0.9% reduction in cardiovascular mortality or hospitalization for HF in a SGLT2i-administered group compared to a placebo group[22]. Kluger *et al*[23] suggests that SGLT2i reduces the rate per 1000 patient-years of primary composite cardiovascular endpoints in patients by 6.5 percent compared with placebo (37.4 *vs* 43.9, respectively). A randomized controlled trial suggested that the relative risk of incident or worsening nephropathy was significantly reduced by 39% in a SGLT2i group compared to a placebo group[24]. Forbes *et al*[25] suggested that SGLT2i reduces the risk of renal failure events by 46% compared with other glucose-lowering substances. Kluger *et al*[23] also suggested that the primary composite renal endpoint occurred in 11.1% of a SGLT2i group *vs* 15.4% in a placebo group (P = 0.00001), doubling of serum creatinine from baseline (sustained for at least 30 days), end stage renal disease [dialysis, renal transplantation, or sustained estimated glomerular filtration rate (eGFR) < 15 mL/minute/1.73 m^2], or renal/cardiovascular death[23]. The effects of SGLT2i can be extended to patients with HF or chronic kidney disease (CKD) without T2DM[26].

While SGLT2i has significant benefits in treating diabetes and related cardiovascular and renal diseases, its use has certain safety concerns. The adverse effects of SGLT2i include genital infections [incidence rate ratio (IRR): 3.50, 95% confidence interval (95%CI): 3.09-3.95], hypotension, diabetic ketoacidosis (IRR: 2.59, 95%CI: 1.57-4.27), an increased risk of lower limb amputation, and an elevated risk of fractures[5,27-29]. Although the incidence of these adverse events is generally low, clinicians should conduct individualized assessments based on the health status of each patient. Therefore, while actively recommending the use of SGLT2i in patients, there is still a need to further evaluate and analyze the risks and side effects of using SGLT2i. Additionally, the use of SGLT2 inhibitors is contraindicated in some patients. For instance, SGLT2i are contraindicated in patients who are allergic to them, canagliflozin and dapagliflozin are contraindicated in patients undergoing dialysis, while all types of SGLT2 inhibitors should be avoided in patients with an eGFR < 30 mL/minute/1.73 m^2[30,31].

Moreover, due to the diversity of patients with T2DM, individual differences in age, complications, and lifestyle should also be considered. Therefore, when using SGLT2i, personalized treatment plans should also be considered. A 2023 study reported similar results for treatment efficacy and safety in older and younger patients treated with SGLT2i[32]. In addition to pharmacological interventions, lifestyle modifications tailored to a patient's individual circumstances, such as dietary adjustments, regular physical activity, and smoking cessation, are crucial for optimizing treatment outcomes and prognoses[33]. These changes not only enhance the efficacy of SGLT2i, but also contribute to better overall health management in patients with T2DM. Personalized plans that include dietary improvements and appropriate exercise can help manage weight, improve cardiovascular health, and support the renal benefits of SGLT2 inhibitors. However, another study revealed that the incremental cost-effectiveness ratio for the addition of SGLT2i therapy to standard-of-care therapy for patients with HFpEF was $141200 per quality-adjusted life-year gain compared to standard-of-care therapy [34]. Therefore, SGLT2i is not applicable for all T2DM patients in terms of economic costs. However, the ability to reduce clinical events and delay disease progression may result in cost savings. In a 2023 economic cost projection study, compared to using sulphonylureas or dipeptidyl peptidase-4 inhibitors as a second-line add-on therapy, SGLT2 inhibitors were shown to achieve cost savings more rapidly for patients with high cardiovascular risk, atherosclerotic cardiovascular disease, comorbid HF, and comorbid CKD (9, 10, 17, 20 years *vs* 14, 16, 23, 23 years)[35]. Therefore, it is necessary to reduce the cost of SGLT2i treatment and alleviate patient difficulties in using SGLT2i treatment; however, this requires further evaluation through real-world research.

CONCLUSION

In general, T2DM is likely to have HF complications, and the use of SGLT2i can effectively treat T2DM patients with asymptomatic HF, which may be related to inhibition of apoptosis or the cardiovascular protective effects of SGLT2i. Meanwhile, SGLT2i can also treat T2DM patients with other comorbidities, which is promising, but more related studies are needed to validate it.

FOOTNOTES

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ORCID number: Yan-Xi Zhang 0009-0009-3320-6789; Hai-Sheng Hu 0000-0001-7873-6956; Bao-Qing Sun 0000-0002-1671-0723.

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