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Flozins in Reducing Cardiovascular and Metabolic Risk: A Literature Review

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Abstract

Introduction

Cardiovascular diseases (CVD) are a significant worldwide health issue, impacting millions of patients and being the primary cause of global illness and death. The combination of SGLT2 inhibitors with weight loss and physical activity can significantly reduce cardiovascular risk. Beyond their primary antihyperglycemic effects, SGLT2 inhibitors elicit pleiotropic benefits including weight loss and favorable alterations in lipid metabolism, culminating in a cardioprotective metabolic environment.

Aim of the study

The aim of the study is to investigate the pleiotropic benefits of SGLT2 inhibitors, including their effects on weight loss, lipid metabolism, and cardiovascular health, in individuals.

Materials and methods

This study presents the current state of knowledge about metabolic and cardiovascular benefits associated with SGLT2 inhibitors in various scientific articles. PubMed database was searched for articles written in English. The search included the keywords „SGLT2-inhibitors"; "SGLT2-inhibitors mechanism of action"; „heart failure"; „cardiovascular events".

Results

SGLT2 inhibitors enhance glycemic control, decrease body weight and visceral fat, and ameliorate several metabolic abnormalities linked to metabolic syndrome, including lipid profile. Clinical investigations have underscored the cardiovascular benefits conferred by SGLT2 inhibitors. Reductions in major adverse cardiovascular events and heart failure-related hospitalizations have been consistently observed, irrespective of diabetic status. Guidelines now advocate for the incorporation of SGLT2 inhibitors as first-line therapies for HFrEF and HFpEF. This endorsement underscores the transformative impact of SGLT2 inhibitors on cardiovascular outcomes.

Key words:

„SGLT2-inhibitors"; " Cardiovascular", „Heart failure"

Pleiotropic Benefits of SGLT2 Inhibitors on Cardiovascular and Metabolic Health – literature review

1. Introduction

The first discovered sodium-glucose transporter (SGLT) inhibitor was phlorizin, a glucoside found in the root bark of apple trees, isolated by de Konink. Von Mering made the observation

that the injection of phlorizin through intravenous insertion resulted in glucosuria, which in turn had a diuretic effect. In the second part of the twentieth century, it was shown in vitro that phlorizin had an inhibitory effect on the transporter, which resulted in glucose reabsorption in the renal proximal tubule as well as in the intestines[1].

Table 1. Tissue expression and biochemical characteristics of sodium–glucose cotransporter 1 and sodium–glucose cotransporter 2. [2]

Characteristics	**SGLT1**	**SGLT2**
Site	Mostly in small intestine some kidney, heart, brain etc.	Mainly in kidney
Renal location	S3 segment of proximal tubules	S1 and S2 segments of proximal tubules
Sugar selectivity	Glucose = galactose	Glucose > galactose
Sodium/glucose stoichiometry	1:2	1:1
Affinity for glucose	High (0.5 mmol/L)	Low (2 mmol/L)
Glucose transport capacity	Low	High

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) have been used as medications for the treatment of diabetes for a long time, and it has only lately been demonstrated that they can improve heart function[3]. Heart failure (HF) is an increasing public health issue that not only decreases life expectancy but also diminishes its quality. Significant progress has been made in treating this disease with the use of several neurohormonal modulators and, more recently, device therapy. However, treating HF is challenging due to its frequent association with various co-morbidities such hypertension, type 2 diabetes mellitus (T2DM), ischemic heart disease, and renal impairment[4].

2. SGLT2-inhibitors

SGLT2 inhibitors act by blocking the sodium-glucose cotransporter subtype-2 in the proximal convoluted tubule portions of the kidney. SGLT2 is a transporter with low affinity but high capacity that is responsible for almost 90% of the reabsorption of filtered plasma glucose, while the remaining amount is reabsorbed by SGLT1[4].

The reabsorption of filtered glucose and sodium is prevented by a SGLT2-inhibition, which leads to glucosuria and natriuresis during the process. Induced urinary glucose loss can result in metabolic adaptations such as decreased fat mass and increased ketone bodies, which serve as an extra source of fuel[5,6].

Other pleotropic benefits of SGLT2-inhibition include a decrease in blood pressure (systolic blood pressure (BP): 1.0–2.6 mmHg; diastolic blood pressure (BP): 0.7–2.2 mmHg) and a reduction in body weight [6], without increases in heart rate[7]. In addition, the unique method of action of SGLT2 inhibitor therapy suggests that it can be administered in conjunction with any of the already available glucose-lowering medications, including insulin, because these drugs do not share any similar molecular pathways during their activity[8] In many cases, it can reduce the amount of insulin required for both type 2 and type 1 diabetes[9,10].

When it comes to the treatment of heart failure, inhibitors of SGLT2 have been shown to have considerable benefits. It has been shown that they minimize the risk of hospitalization for heart failure while reducing symptoms in people with T2DM and heart failure, regardless of diabetes. Their diuretic effect, reduction in preload and afterload, and potential impact on myocardial energy metabolism are responsible for this effect[11].

SGLT2 inhibitors reduce the renal threshold for glucose. Their glucosuric effect is self-limiting, ensuring that they do not cause clinically significant hypoglycemia. This is because, as the inhibitor induces increased glucosuria, blood glucose levels fall, resulting in reduced filtration. Adequate active transporters are capable of reabsorbing nearly all of this diminished glucose, thereby preventing blood glucose levels from falling below euglycemia[12]. SGLT2 inhibitors have also been associated to lower intraglomerular pressure within the kidneys. These medications can potentially delay the progression of diabetic kidney disease by reducing the glomerular load. Decreased intraglomerular pressure may also contribute to preserving glomerular filtration rate (GFR) in patients with impaired renal function[13].

Studies on SGLT2 inhibitors have shown that the synthesis of glucose by the liver rises when the concentration of glucagon in the blood increases. Both SGLT2 and -1 isoforms are present in pancreatic alpha islet cells. As a result, the presumed actions of SGLT2 inhibitors on pancreatic islet cells entail directly inhibiting SGLT2 or triggering compensatory glucagon production when glucose levels decrease. Nevertheless, the outcomes have been variable due to variations in SGLT2 expression across different models. Within an animal model, SGLT1 was the primary type found in the α islet cells. It stimulated the release of glucagon through α islet cells when treated with dapagliflozin. Solini et al. also showed that αTC-1 cells with reduced SGLT2 expression had an elevation in glucagon secretion following dapagliflozin therapy[14,15].

In addition to their weight-reducing effects, these lipid modifications lead to a more cardioprotective metabolic profile. In conclusion, the action mechanisms of SGLT2 inhibitors extend far beyond their primary function in glucose regulation. Their impact on glucose

excretion, blood pressure reduction, vascular health, and the management of heart failure demonstrates their critical role in improving cardiovascular and renal outcomes in individuals with T2DM and beyond.

3. Diabetes mellitus and cardiovascular diseases

Given that cardiovascular disease is the leading cause of death and illness in diabetic populations[16], a key objective of diabetes management should be to enhance the cardiovascular risk profile of diabetic patients. Treating diabetes mellitus and minimizing cardiovascular events is challenging due to the complex and multidimensional connection between diabetes mellitus and cardiovascular disease. Cardiovascular disease risk factors such as obesity, hypertension, and dyslipidemia are prevalent in people with diabetes mellitus, especially those with type 2 diabetes[17]. Diabetic people are at a higher risk of developing cardiovascular disease due to the combination of high rates of cardiovascular risk factors and the direct biological effects of diabetes on the cardiovascular system. This contributes to the increased occurrence of myocardial infarction (MI), revascularization, stroke, and congestive heart failure (CHF)[16]. Insulin resistance in Type 2 Diabetes Mellitus (T2DM) leads to changes in lipid metabolism that accelerate the development of atherosclerosis. Insulin resistance can also result in hypertension, a significant risk factor for cardiovascular disease. Prolonged high blood sugar in diabetes can lead to microvascular problems such as retinopathy, nephropathy, and neuropathy. It speeds up the development of atherosclerosis and raises the possibility of macrovascular issues such as coronary artery disease (CAD), stroke, and peripheral arterial disease (PAD)[18].

4. Weight loss and lipid metabolism

Type 2 diabetes mellitus is closely associated with obesity, a condition that has become more and more common worldwide. Visceral fat buildup decreases hepatic insulin clearance, leading to hepatic neoglucogenesis[19]. As obesity is a major risk factor both for CVD and T2DM, many studies have investigated the efficacy of weight loss in reducing the development and severity of DM. Given the benefit of SGLT2i on the reduction of body weight, it may be helpful in T2DM patients who are overweight or obese, especially patients taking other medications that can cause weight gain. SGLT2i has been shown to result in a slight reduction in body weight compared to placebo. A meta-analysis comparing SGLT2i with placebo has reported that a reduction of body weight was observed in SGLT2i users compared to placebo. Obesity is a significant risk factor for both cardiovascular disease (CVD) and type 2 diabetes (T2DM).

Numerous research have examined how effective weight loss is in decreasing the occurrence and seriousness of diabetes mellitus (DM). SGLT2 inhibitors may be beneficial in overweight or obese individuals with type 2 diabetes, particularly those who are taking drugs that can lead to weight gain, due to their ability to reduce body weight. A meta-analysis comparing SGLT2 inhibitors with a placebo found that SGLT2 inhibitor users saw a decrease in body weight compared to those taking the placebo[20].

The potential mechanisms of weight reduction from SGLT2 are believed to result from an increase in the urinary glucose excretion[21]. Overall body weight reductions are thought to be caused by caloric loss and the stimulation of lipolysis, which results in fat loss.[22]. Research on body composition has demonstrated that over two-thirds of long-term weight loss can be attributed to the reduction of body fat[23].

SGLT2 inhibitors have a major impact on lipid metabolism, working at several cellular levels. They reduce lipid accumulation, visceral and subcutaneous fat, not only lowering body weight but also changing body composition. They also regulate key molecules involved in lipid production and transport, as well as fatty acid oxidation. Notably, they change the substrate utilisation from carbohydrates to lipids and ketone molecules[22]. Diabetic dyslipidemia is characterized by elevated triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and increased tiny, dense, low-density lipoprotein (LDL). This lipid profile increases the risk of cardiovascular disease[24].

5. Major adverse cardiovascular events (MACE).

The cardioprotective effects of SGLT2 inhibitors have been demonstrated by landmark trials such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58, which were particularly concerned with the reduction of major adverse cardiovascular events (MACE).

In the EMPA-REG OUTCOME trial ([Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) in patients with T2DM and ASCVD, the sodium glucose cotransporter 2 inhibitor empagliflozin given in addition to standard of care reduced the risk of 3-point MACE (composite of cardiovascular death, nonfatal MI, or nonfatal stroke) by 14%, cardiovascular death by 38%, all-cause death by 32%, and hospitalization for heart failure (HHF) by 35% in comparison with placebo. ASCVD was defined as a prior atherothrombotic event (MI or stroke) and other vascular manifestations of ASCVD (multivessel coronary artery disease; single-vessel coronary artery disease with ischemia and unstable angina ≤12 months before consent or occlusive peripheral artery disease)[25].

CANVAS program: The CANVAS program evaluated canagliflozin, another SGLT2 inhibitor, in patients with T2DM and a high risk of CVD. This program shown a 14% reduction in rates of major adverse cardiovascular events in participants assigned to canagliflozin compared with placebo-treated participants, primarily driven by a reduction in the risk of non-fatal MI[26].

The Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 trial: The DECLARE-TIMI 58 trial examined dapagliflozin in a broader population of patients with T2DM, including those without documented CVD. Although the primary endpoint of major adverse cardiovascular events (MACE) reduction was not accomplished, there was a significant decrease in hospitalization for heart failure[27].

6. Heart failure

Heart failure is a condition characterized by symptoms and signs that result from cardiac dysfunction, leading to decreased life expectancy. To establish a diagnosis of heart failure, the European Society of Cardiology guidelines warrant the existence of symptoms and signs, objective evidence of cardiac dysfunction (preferably by echocardiography), and a positive response to heart failure treatment in cases of uncertainty. Diagnosing heart failure based only on symptoms and indications, which is common in basic care, is challenging. Many patients diagnosed with heart failure may actually be obese, have a poor physical condition, pulmonary disease, or ischemia on further examination. Increasing evidence suggest that if natriuretic peptide levels are normal and the electrocardiogram is normal, it should lead to a reconsideration of a diagnosis of heart failure[28].

Several clinical trials examined the effectiveness of SGLT2 inhibitors in patients with heart failure with reduced ejection fraction (HFrEF). The DAPA-HF and EMPEROR-REDUCED studies have shown substantial advantages in decreasing morbidity and death linked to heart failure[29,30].

The DAPA-HF trial was a significant study that evaluated the impact of dapagliflozin, an SGLT2 inhibitor, on HFrEF patients with or without type 2 diabetes. 4,744 patients were included in the experiment. The results showed that dapagliflozin decreased the likelihood of the composite primary outcome (consisting of cardiovascular mortality, hospitalization for heart failure, or an urgent visit for heart failure) by 26% when compared to the placebo group.[29]. The EMPEROR-REDUCED trial examined empagliflozin, different SGLT2 inhibitor, in 3,730 HFrEF patients. The experiment showed that empagliflozin significantly decreased the risk of cardiovascular death and hospitalization for heart failure by 25%, compared to the placebo group, regardless of whether the participants had diabetes or not[30].

Heart failure with preserved ejection fraction (HFpEF) s the predominant kind of heart failure. Making an HFpEF diagnosis is complicated. These patients typically not have an enlarged left ventricle (LV), but they frequently display a thickening LV or increased myocardial mass and/or enlarged left atrium as an indication of elevated filling pressures. Most have additional signs of decreased left ventricular filling or suction capacity, known as diastolic dysfunction, which is widely recognised as the probable reason for heart failure in these patients. [31]. HFpEF is diagnosed when a patient displays symptoms of heart failure, has a left ventricular ejection fraction (LVEF) of 50% or higher, has ruled out conditions that mimic heart failure (such as lung disease, pulmonary embolism, pulmonary hypertension, and renal disease), and shows signs of increased pressure in the left ventricle or elevated levels of natriuretic peptides[32]. Compared to HF with reduced ejection fraction (HFrEF), there are few established treatments that provide cardiovascular (CV) benefits in HFpEF[33]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are known to decrease the development and progression of HFrEF[34]; however, the effect of SGLT2 inhibition in patients with HFpEF remains unclear. Given this uncertainty, the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved) was performed to evaluate the effects of SGLT2 inhibition with empagliflozin in patients with HFpEF[35].

The EMPEROR- In patients with heart failure and a preserved ejection fraction, SGLT2 inhibition with empagliflozin resulted in a 21% reduction in the combined risk of cardiovascular death or hospitalization for heart failure. This was primarily caused by a 29% decrease in the risk of hospitalization for heart failure with empagliflozin. The impact on the occurrence of primary endpoint events was consistently observed in all predetermined subgroups, regardless of whether patients had diabetes or not. Empagliflozin resulted in a decreased overall number of heart failure hospitalizations and an extended duration until the first heart failure hospitalization [35].

DELIVER trial - The study showed comparable outcomes to the EMPEROR-Preserved trial, with a notable 18% decrease in heart failure hospitalizations with dapagliflozin (HR 0.82; 95% CI 0.73-0.92, P <.001) and no significant variance in cardiovascular mortality. Among patients with an ejection fraction (EF) greater than 60%, the results for the combined primary outcome were in line with the overall findings. The DELIVER study's unique results imply that the benefits of SGLT2 inhibitors may extend to those with higher ejection fraction and NYHA class II to IV symptoms, contrary to previous findings indicating a decrease in effectiveness when ejection fraction is above 60%. The DELIVER study enhanced the findings of EMPEROR-

Preserved and reinforced the efficacy of SGLT2 inhibitors in reducing hospitalizations in patients with heart failure with preserved ejection fraction (HFpEF).[36].

7. Current guidelines of using SGLT2 inhibitors in Chronic Heart Failure

SGLT2 inhibitors are currently recognized as heart failure reduced ejection fraction first-line treatment in heart failure and should be first line for diabetic and should be initiated in all HFpEF patients without contraindications, ideally once stable during hospitalization for index event[37]. In the 2021 ESC Guidelines there were no recommendations on the use of sodium–glucose co-transporter 2 (SGLT2) inhibitors in patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) as no trials had been conducted in these groups. Since then, the EMPEROR-Preserved trial and the DELIVER trial were conducted with the SGLT2 inhibitors empagliflozin and dapagliflozin, respectively. The focused update recommends an SGLT2 inhibitor (dapagliflozin or empagliflozin) in patients with HFmrEF and HFpEF to reduce the risk of heart failure hospitalisation or cardiovascular death. According to ESC Guidelines 2023, In both patients with heart failure with mildly reduced ejection fraction (HFmrEF) and in patients with heart failure with preserved ejection fraction (HFpEF) , the use of a sodium-glucose cotransporter 2 (SGLT2; dapagliflozin or empagliflozin) inhibitor is recommended to reduce the risk of hospitalization or death from cardiovascular causes[38].

8. Conclusions

The introduction of SGLT2 inhibitors marks a significant milestone in the management of type 2 diabetes mellitus (T2DM) and cardiovascular diseases. By blocking glucose reabsorption in the kidneys, they not only improve glycemic control but also induce weight loss and lipid modifications, leading to a cardioprotective metabolic profile. Clinical trials have demonstrated their efficacy in reducing heart failure-related hospitalizations and cardiovascular events. Guideline recommendations now support their use as first-line treatments for heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Overall, SGLT2 inhibitors offer a comprehensive approach to managing T2DM and cardiovascular conditions, improving outcomes and the prognosis for patients.

After conclusions

Author's contribution:

Conceptalization: Julia Sieniawska, methodology: Patrycja Proszowska, software, Daria Sieniawska, check: Patrycja Proszowska, formal analysis: Patrycja Proszowska, investigation: Julia Sieniawska, resources, Daria Sieniawska, data curation, Patrycja Proszowska, writing-rough preparation, Daria Sieniawska, visualization, Patrycja Proszowska, supervision, Julia Sieniawska, project administration, Daria Sieniawska

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