Sodium-Glucose Co-Transporter 2 (SGLT-2) Inhibitors in Heart Failure: A Comprehensive Review of Literature

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is highly prevalent in the modern world due to a rise in obesity. Diabetes can give rise to many secondary ailments among which heart failure is the most common. Heart failure brings about confirmatory changes in the myocardium which shifts the metabolism from glucose to fatty acid which further impairs cardiac function. Among the antidiabetic agents, SGLT2 inhibitors such as empagliflozin and dapagliflozin have decreased heart failure exacerbations even in the absence of diabetes. We employed search engines such as Google Scholar, MEDLINE, and Euro PMC for our article search. The keywords such as heart failure, SGLT2 inhibitors, and diabetes were used. Duplicate studies were excluded during our analysis. According to the literature, several theories have been put forward on the mechanisms through which SGLT2 inhibitors can work in heart failure. Mainly they work by lowering blood pressure, improvement of cardiac energy metabolism, anti-inflammatory effect, protecting from cardiac remodeling, diuresis, and natriuretic effects.

Keywords: *Heart failure, sodium-glucose transporter 2 inhibitors, diabetes mellitus, metabolism, diuresis.*

INTRODUCTION

The incidence of type 2 diabetes mellitus (T2DM) has been on the rise globally due to the increase in the prevalence of obesity [1]. The mechanism behind T2DM is based on impaired beta-cell function, increased hepatic glucose output, and insulin resistance in muscles and adipose tissues [2]. Diabetes mellitus is often a contributing factor in the development of heart failure and it is reported that around 45% of patients with preserved and 40% with reduced ejection fraction have diabetes. Heart failure (HF) causes a change in myocardial metabolism, shifting its metabolism to glucose from fatty acid. In diabetes, due to the suppression of fatty acid oxidation, myocytes are forced to oxidize glucose which is further impaired because of insulin resistance thereby impairing cardiac functionality [3]. Cardiovascular death (CV) is the leading cause of death among diabetic patients, resulting in frequent hospitalizations due to exacerbation and decreasing quality of life. Treatment of diabetes in heart failure is targeted to increase beta-cell activity and also restore insulin sensitivity which is facilitated by many pharmacological agents and drug types. Unfortunately, diabetic medications such as peroxisome proliferator-activated receptor gamma (PPAR gamma) agonists and dipeptidyl peptidase-4 inhibitors, it has been observed that increase HF hospitalizations [4]. Despite this unfavorable outcome of other medications, the sodium-glucose transporter-2 (SGLT-2) inhibitors have proven to be effective. These drugs have been shown to decrease cardiovascular mortality by 38%, which is thought to be because of a reduction in HF exacerbations. This monumental decrease in CV mortality has garnered significant interest in SGLT-2 inhibitors and their benefits in treating heart failure even in the absence of concurrent diabetes. There have been several large-scale clinical trials to evaluate the effectiveness and safety of SGLT2 inhibitors, especially in patients with established heart failure. The brilliant results of the EMPA-REG OUTCOME study demonstrated an early reduction in major cardiovascular and renal outcomes in diabetic patients with a high risk of cardiovascular disease [5, 6].

METHODS

A comprehensive literature search was conducted by the investigators (AYK and HZK) independently. The literature databases such as Google Scholar, PubMed, and Web of Science were searched from December 20th to January 4th by using the combination of keywords such as SGLT2 inhibitors, heart failure, ejection fraction, mortality, and Sodium-glucose co-transporter. It is worth mentioning that only articles that were original studies, review articles, had full text available, and were written in English were considered for our review. The initial search results were then scrutinized for relevance, language, full-text availability, and appropriateness. The initial search returned with 89 articles and after excluding articles for our criteria we were left with 48 articles (**Fig. 1**).

DISCUSSION

### Renal Sodium and Glucose Physiology
The human kidney has a remarkable capacity for filtration. It filters around 180g of glucose daily. The proximal convoluted tubule reabsorbs glucose, which is proportional to plasma glucose concentration and the glomerular filtration rate (GFR). As soon as the maximum

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│  Articles searched in  databases with │
│         relevant keywords: 89         │
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│  Articles excluded due to not having  │
│         a full text: 23               │
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Fig. (1): Flow chart of study selection.

absorption capacity is reached there is a linear rise in glucose excretion. This system usually does not reach full capacity in non-diabetic individuals [7]. The proximal convoluted part of the nephron absorbs glucose back into circulation through a biphasic process. The sodium-glucose co-transporter 1 & 2 absorb glucose against the concentration gradient at the expense of energy provided by Na+/K+ ATPase. In the next phase, GLUT2 transporters absorb glucose into the circulation [8]. Chronic hyperglycemic state in diabetic patients increases the transport maximum by 40% due to the hyperactivity of SGLT2 in kidney tubules which leads to these individuals retaining more glucose. In 1987, Rossetti *et al.* demonstrated that phlorizin could compete with SGLTs 3000 times higher than glucose. In the intestinal tract, SGLT1 inhibition causes diarrhea which makes phlorizin an unsuitable molecule clinically. This prompted an undistributed focus of research on drugs that would block SGLT2 preferentially (**Fig. 2**) [9, 10].
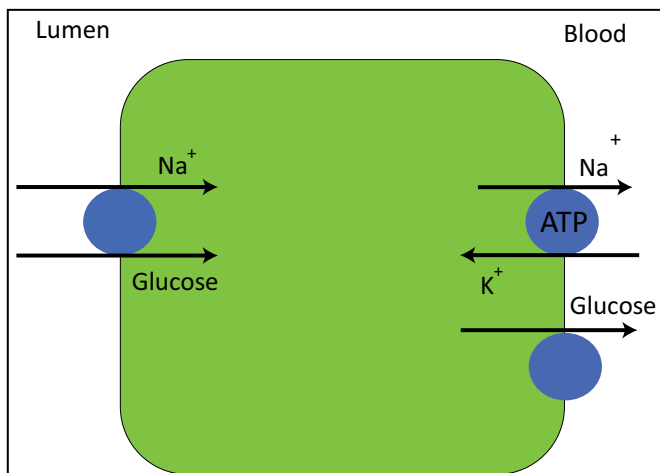
Fig. (2): A schematic diagram depicting the interplay between the tubular lumen and blood through the SGLT2 transporter.

Clinical Effects of SGLT2 Inhibition

Mainly, the blockage of SGLT2 receptors reduces the threshold of the kidney to excrete glucose thereby permitting its removal from the body even in the setting of normal glucose levels [8]. Though, not completely but a resultant increase in expression of SGLT1 counters the weight loss and glycosuric effect but there is a clinically significant glycosuria effect observed [11]. In clinical studies, there is a reduction of approximately 0.6%-0.8% reported when compared to placebo which is biologically plausible as lower HbA1c levels result in patients having to spend comparatively less time in hyperglycemia which does not completely saturate the transport through SGLT2 receptors [12]. In the context of heart failure, the interesting aspect is the concomitant sodium absorption in a 1:1 ratio therefore a significant natriuretic effect is seen in SGLT2 blockage. In addition to the glycosuric effects, SGLT2 inhibition is shown to reduce systolic blood pressure by about 3-4 mmHg [13]. A study comparing dapagliflozin against hydrochlorothiazide and placebo showed that the SGLT2 inhibitor has a diuretic-like effect which lowers the blood pressure and also demonstrated that a 12-week course of dapagliflozin was associated with 24-hour blood pressure readings that were comparable with hydrochlorothiazide. There have also been signs of reduction in glomerular filtration rate on initiation of SGLT2 inhibitor treatment but this effect gets blunted after some time [2].

Cardioprotective Mechanisms of SGLT2 Inhibition

There have been several theories put forward to explain how the SGLT2 inhibitors can be beneficial. These effects are based on the following physiologic phenomena:

1. Lowering of blood pressure, 2. Improvement of cardiac energy metabolism, 3. Anti-inflammatory effect, 4. Weight loss, 5. Inhibition of the sympathetic nervous system, 6. Cardiac fibrosis and remodeling, 7. Uric Acid, 8. Diuresis and Natriuretic effects, and 9. Autophagy.

1. Lowering Blood Pressure

Hypertension is a commonly encountered problem in patients with type 2 diabetes mellitus which requires them to take an antihypertensive agent. The guidelines recommend that a targeted blood pressure of <140/90 mmHg should be maintained to for protecting against micro and macrovascular complications, disability, and death. This target however is further decreased for patients having concomitant chronic kidney disease, or maybe at higher risk for developing cardiovascular disease [14]. Even though SGLT2 inhibitors are not primarily antihypertensive drugs but they are indeed known to lower the systolic and diastolic blood pressure by 4-6 mmHg and 1-2 mmHg respectively [15]. The main mechanism behind this reduction is not clearly understood but it is postulated that this could be based on the osmotic and diuretic effect of the SGLT2 inhibitors. It is worth noting that SGLT2 inhibition can cause a 30-60% increase in the

excretion of urinary sodium. The antihypertensive effect of SGLT2 inhibition is greater than that of thiazide combined with a beta-blocker or calcium antagonist; this profound reduction decreases cardiac afterload and results in the enhancement of cardiac efficiency [16, 17]. SGLT2 inhibition also improves vascular function which also contributes to blood pressure improvement along with cardiac function by reducing afterload. A post-doc analysis concluded that dapagliflozin reduces blood pressure and decreased vascular resistance and arterial stiffness [18].

2. Improvement of Cardiac Energy Metabolism

In the event of heart failure, there are energy changes taking place such as the shift in dependence from mitochondrial oxidative metabolism to glycolysis as the primary source of energy. In a failing heart, oxidation decreases leading to a dramatic decrease in energy production which starves it [19]. The reduction in the efficiency of the heart is not limited to patients with heart failure with reduced ejection fraction but also occurs in patients with preserved ejection fraction hearts that have hypertrophy and reduced left ventricle capability [20]. The SGLT2 inhibitors improve cardiac energy metabolism by increasing circulating ketone levels which are due to the mobilization of adipose tissue as they are then used for ketogenesis by the liver [21]. This rise in ketone levels due to SGLT2 inhibition can occur even in the absence of diabetes [22]. These ketone bodies nonetheless are not considered to be an efficient fuel source for the heart instead they act as an additional source of energy in an otherwise fuel-deficient failing heart [19]. The heart adapts by increasing ketone oxidation and increasing ketone levels with SGLT2 inhibitor drugs, improving the supply of energy [23]. The study has shown that an empagliflozin-induced increase in ketone oxidation is linked to the enhancement of cardiac performance. Empagliflozin also decreases adverse remodeling of a failing heart in porcine models [24].

3. Anti-Inflammatory Effect

Heart failure is linked to inflammation and proinflammatory biomarkers which correlate with the severity of the disease [25, 26]. This correlation with inflammation applies to heart failure with preserved and reduced ejection fraction [27]. In heart failure inflammation initiates from danger-associated molecular patterns (DAMPs) which are indicative of cellular damage and are shown to play an integral role in inducing certain irreversible changes in myocardial cells such as fibrosis, cellular death, ischemia, and oxidative stress [28]. Ischemia, reperfusion injury, and other causes of oxidative stress cause the production of reactive oxygen and nitrogenous products which function as DAMPs

that are linked to ventricular remodeling [29]. The increased ventricular filling pressures, congestion, and shear stress lead to myocardial injury, and molecules released as a byproduct are detected by immune cells as DAMPs which further cause inflammation in heart failure [30, 31]. The NLRP3 inflammasome which is a complex of intracellular proteins recognizes DAMPs and initiates the maturation of proinflammatory cytokines. The activated inflammasome converts pro-caspase-1 into caspase-1 which in turn activates IL-1 and other proinflammatory cytokines such as IL-1 β and IL-18 by cleavage of their inactive forms [29]. The work done by Kim *et al.* has shed some light on the mechanism behind the SGLT2 inhibition of NLRP3 inflammasome activity. They demonstrated that by inhibiting SGLT2, a significant suppression of NLRP3 activation and secretion of IL-1 β was observed which was secondary to increased serum levels of beta-hydroxybutyrate. The glycosuria due to SGLT2 inhibition causes a state of hypoinsulinemia which reduces tissue glucose uptake. This reduced glucose uptake enhances lipid oxidation thus giving rise to serum beta-hydroxybutyrate levels [32].

4. Weight Loss

SGLT2 inhibitors promote the removal of 60-80g of glucose through the kidney per day which causes a significant loss of 240-320 calories daily leading to a considerable weight loss of 2-4 kilograms [33]. According to dual-energy x-ray absorptiometry studies, 60-70% of the weight loss seen with dapagliflozin was in the adipose tissue of both the visceral and subcutaneous tissue which is estimated on the magnetic resonance imaging data [34]. A study found that glycosuria is persistent but the resultant weight loss approaches a plateau and it is lower than the caloric loss observed daily. This discrepancy observed distinguishes this weight loss from that seen with Glucagon-like peptide receptor 1 agonist [35]. The clinical data suggest that weight loss due to SGLT2 inhibitors varies heavily according to body mass index (BMI). Some studies suggest a higher weight loss in higher BMI patients though this result was not observed consistently. The trials investigating weight loss with ipragliflozin and canagliflozin found that weight loss is observed also in patients with low BMI, on the other hand, a 53-week study investigating luseogliflozin observed higher weight loss in participants with higher BMI [33, 36]. Nonetheless, the SGLT2 inhibition-related weight loss is moderate and has the possibility of diminishing over time as counter-regulatory methods activate to maintain the body weight. It is also worth mentioning that weight loss alone has not been much effective in decreasing heart failure therefore other mechanisms must also be involved [36].

5. Control of the Sympathetic Nervous System

The sympathetic nervous system is shown to play a role in several chronic conditions such as heart failure, hypertension, type 2 diabetes, ischemic heart disease, *etc.* It is also highly associated with a poor prognosis in heart failure because it has a devastating effect on the vasculature and also plays a role in remodeling. In patients with type 2 diabetes mellitus, a higher heart rate increases mortality and unfavorable outcomes [37]. It has been observed in real-world practices that patients on SGLT2 inhibitors have a reduction in heart rate. In a clinical trial investigating luseogliflozin it was seen that patients with a resting heart rate of more than 70 mmHg had a larger decrease in heart rate after the treatment when compared to the patients having that ≤ 70 mmHg [38, 39]. This observation is highly suggestive of the idea that SGLT2 inhibitors affect the sympathetic nervous system. Indirectly this reduction in sympathetic activity can also be in part due to reduced tyrosine hydroxylase production and decreased norepinephrine turnover in brown adipose tissue [40]. Another noteworthy finding in the literature suggests that this effect can also be explained by the reduction in the nephrology stress secondary to renal afferent sympathetic inhibition [37].

6. Cardiac Remodeling and Fibrosis

As heart failure is a heterogenous entity, the mechanism, and outcomes of ventricular remodelling are diverse and thus, the clinical outcome. Despite multiple lines of treatments and advancement in technology in the forms of devices, the majority of the patient population have a progressive decline in left ventricular functionality [41]. Heart failure patients remain asymptomatic after an initial decline of left ventricular contractility as a result of the compensatory mechanism which leads to complex functional and structural abnormalities of myocytes and also non-myocyte elements enlarging the left ventricular cavity causing dysfunction [42]. On the molecular level, cardiomyocyte hypertrophy and extensive extracellular matrix production are not only promoted by chronic mechanical overload, and ischemia but also by the original etiology such as necrosis, virus, autoimmunity *etc.* [42]. Myocardial re-modelling also includes non-myocardial cells and extracellular matrix (ECM). ECM includes fluids, collagen, and glycoprotein. In heart failure, cardiac interstitium increases due to interstitial fibrosis, post-necrotic replacement fibrosis, myocardial edema, or pathological infiltration in the form of amyloid. The renin-angiotensin-aldosterone system is vital for the activation of fibroblasts and collagen deposition with downstream signaling of transforming growth factor B. Certain cardiac biomarkers can be useful in gauging the extent of cardiac remodelling which are established through evidence-based principles [43].

SGLT2 inhibition is implicated in the remodeling of a failing heart, particularly the left ventricle. The monumental placebo-controlled EMPA-HEART study which comprised 97 participants with diagnosed type 2 diabetes, coronary artery disease, and a preserved ejection fraction, concluded based on cardiac MRI that SGLT2 inhibition results in a reduction in the left ventricular mass index after 6 months of treatment, and this finding was not associated with blood pressure alterations. In another study which was an uncontrolled trial, it was revealed based on echocardiography that SGLT2 inhibition is linked to an improved diastolic function [44]. Fibrosis is considered to play a major pivotal role in the remodeling of a failing heart and according to an animal model of myocardial infarction SGLT2 inhibition influences myofibroblasts and macrophage infiltration which then translates into an anti-fibrotic effect. Empagliflozin is also reported to suppress the profibrotic mechanisms based on type 1 collagen, actin, connective tissue growth factor, and matrix metalloproteinases. A key target of empagliflozin is AMP-activated protein kinase (AMPK) which is an enzyme that has a role in metabolic homeostasis and anabolism. AMPK further plays a protective role in mitochondria by suppressing inflammation, apoptosis, and fibrosis [44].

7. Uric Acid

Uric acid is made in the final steps of purine nucleotide degradation and it has been linked to cardiovascular disease. SGLT2 inhibitors decrease uric acid levels by causing robust glucosuria which further suppresses urea resorption in the nephrons [45]. Hyperuricemia can be associated with increased inflammation, oxidative stress, and endothelial dysfunction [46]. Existing evidence suggests that SGLT2 inhibitors have been proven to decrease uric acid levels in diabetic patients. These changes were however not seen in chronic kidney disease patients [47].

8. Natriuresis and Diuresis

These medications are a promising source for inducing natriuresis and glucosuria and this osmotic diuresis is considered to improve the heart failure symptoms and prognosis. The EMPA-REG study suggested that the resultant hemoconcentration which is secondary to the diuresis is responsible for 50% of the cardiovascular effects [5]. Even though it cannot be said with certainty that the benefits of SGLT2 inhibitors are largely due to the robust diuresis alone because other medications in the same class have been observed to be different such as a trial that compared hydrochlorothiazide and dapagliflozin showed that an increase in red blood cell mass was observed with the SGLT2 inhibitor while no such finding was seen in the thiazide group [48]. In another similar study albeit, a comparison of dapagliflozin

with a loop diuretic bumetanide, the former caused a reduction in interstitial volume while the latter acted on the intravascular compartment [49]. These contrasting findings prompt us to infer that SGLT2 inhibitors have a different action where they regulate interstitial volume which restricts the neurohumoral activation that may occur with intravascular volume reduction with other diuretics [40].

CONCLUSION

In today's age with the rise in obesity, there is also a rise in the incidence of type 2 diabetes mellitus. There is a large number of diabetic patients who develop concomitant heart failure which poses a therapeutic challenge to clinicians. Anti-diabetic agents such as SGLT2 inhibitors represent a distinguished class of drugs proven to be of value in the treatment of heart failure and diabetes. Several mechanisms have been elucidated which have been found to play a vital role in the management of heart failure. These mechanisms are diverse and range from diuresis, cardiac remodeling, weight loss, cardiac energy metabolism, and lowering of blood pressure. Based on the trials, it can be suggested that these drugs are here to stay in the management of heart failure and they also hold a great deal of potential in the future of heart failure treatment.

CONFLICT OF INTEREST

Authors do not have any conflict of interest to disclose.

AUTHORS' CONTRIBUTION

AYK conceptualized, searched the literature, and wrote the draft, HZK searched the literature, wrote the draft, and created the figure.

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