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Original Article

SGLT2 Inhibitors: Pharmacology and Expanding Role Beyond Diabetes

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ABSTRACT

SGLT2s are a new type of oral diabetes treatment that work by preventing glucose from being absorbed through the kidneys, which helps the body get rid of extra glucose through the urine. Unlike traditional ways to treat diabetes, SGLT2 inhibitors work without using insulin, so people taking this type of medicine can manage their blood sugar levels with less chance of developing low blood sugar (hypoglycemia). SGLT2 inhibitors also may help people lose a small amount of weight and maintain lower blood pressure. The benefits of taking SGLT2 inhibitors go beyond just controlling blood sugar levels. Clinical studies are showing that SGLT2 inhibitors help protect the heart and kidneys. In fact, large studies of patients with heart failure have found that SGLT2 inhibitors reduce the risk of being hospitalized for heart failure; slow down the progression of chronic kidney disease; and lower the risk of dying from cardiovascular causes, even in people who do not have diabetes. The additional benefits of taking SGLT2 inhibitors may be due to blood flow changes throughout the body, including the way the heart works, how the body metabolizes food, and how inflammation occurs in the body. Although SGLT2 inhibitors can cause unwanted effects (such as infections in the genital area or very rarely euglycemic diabetic ketoacidosis), the overall benefits of taking SGLT2 inhibitors greatly outweigh the risks if the right patients are chosen and monitored closely. This expanding role for SGLT2 inhibitors in combination with other medications (for example, when treating patients with diabetes, high blood pressure, and/or high cholesterol) makes them very important in providing integrated care across the cardio-renal-metabolic spectrum.

Keywords: SGLT2 Inhibitor, Diabetes Mellites, Heart Attack, Protection, Weight Loss

INTRODUCTION

Diabetic patients have increased significantly in recent decades, mainly due to the rise in type 2 diabetes mellitus (T2DM). This trend leads to serious health, economic, and social challenges. [1] Treating diabetes is expensive, and the annual costs are rising. There are many antidiabetic drugs available that can be used alone or together. Each drug works differently, and its effects can change based on several factors, including the dose. Antidiabetic drugs aim to control glucose metabolism, primarily by lowering blood sugar levels. Consequently, many of these drugs may also help treat other conditions, especially obesity, which is a key contributor to diabetes mellitus (DM). [2] As a result, the variety of available drugs, their mechanisms, and biological effects have sparked much discussion across different health fields, including cardiovascular, kidney, neurological, and cancer-related areas. [3] Because diabetes is a complex disease, it requires a careful study when looking for new treatment targets or understanding how medications with potential antidiabetic effects work. [4] Furthermore, some, if not all, of these drugs can change cellular metabolism in ways that might help some organs but harm others. This presents a complicated challenge that hinders progress. [5] It has been noticed earlier that SGLT2 inhibitors are useful for increasing blood pressure, serum triglyceride levels, and body weight respectively [6–8]. The diabetic population is mostly prone to other factors of metabolic syndrome including cardiovascular diseases, and a protective role of SGLT2 inhibitors has been noticed for such conditions [9-11]

2. Role in Glycemic Management of Type 2 Diabetes Mechanism

SGLT2 cotransporters are located in the early PCT of the kidney, where they perform active glucose

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reabsorption in order to maintain optimum blood glucose levels [12]. SGLT2i medications act in an insulin-independent manner to selectively inhibit the reabsorption of glucose in the kidney and promote excretion via the urine [12]. Currently, three SGLT2i therapies are available for clinical use in the UK for the treatment of T2DM: canagliflozin (distributed in the UK by Napp Pharmaceuticals Limited), dapagliflozin (AstraZeneca UK Limited) and empagliflozin (Boehringer Ingelheim Limited) [13,14,15]. From a pharmacological perspective, all three therapies are very similar with regard to their mechanisms of action, although canagliflozin is known to also have affinity for SGLT1 cotransporters located in the suggest that this property may be important to the enhanced postprandial glucose-lowering action of canagliflozin 300 mg compared with canagliflozin 100 mg [13] intestine and kidneys [13]. Phase 3 studies.

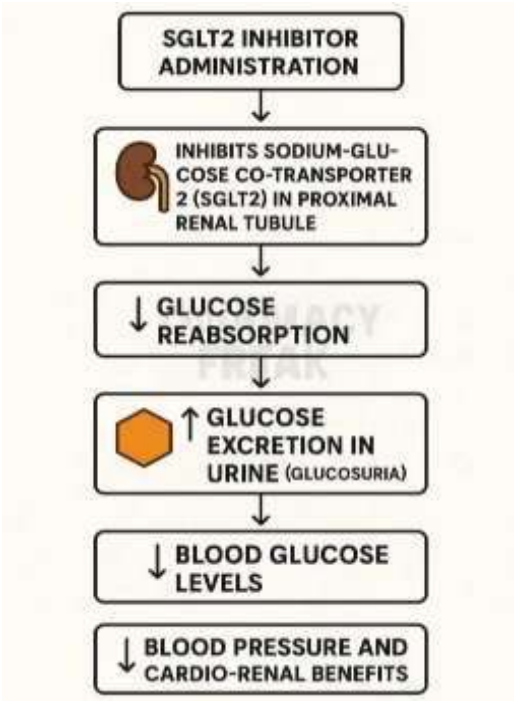

Figure 1: Mechanism of SGLT2 Inhibitor [16]

3. Heart Failure Epidemiology in Type 2 Diabetes

Type 2 diabetes mellitus (T2DM) is a complex chronic illness that affects many systems throughout the body. Recent increases in T2DM parallel the increase in the number of people who are obese or have sedentary lifestyles. Individuals with T2DM also face an increased risk for many different types of cardiovascular disease (CVD), with heart failure (HF) being more common as an initial diagnosis than myocardial infarction (MI) [17]. It has been estimated that 9% to 22% of patients with T2DM will have HF; this figure is likely higher for individuals over 60 years of age [18,19,20,21]. Patients with T2DM are at increased risk for HF; this risk is close to double that for patients without T2DM. Many different factors can affect how likely a patient with T2DM will develop HF [22]. Disease duration, obesity, hypertension, coronary artery disease (CAD), peripheral arterial disease (PAD), diabetic nephropathy (nephropathy caused by diabetes), diabetic retinopathy (retinopathy from diabetes), and levels of NT-Probing (an indicator of heart failure) are all risk factors that increase the likelihood of developing HF in T2DM patients [23,24,25]. Additionally, in a study done in Framingham, it was observed that the risk for HF was much greater for women than for men, with women being five times more likely to develop HF when compared to diabetic men [26]. Patients with HF are frequently insulin resistant, and may experience higher blood glucose levels and/or develop diabetes as a result of their HF [27]. Many studies have demonstrated that HF is common in patients with T2DM; 30%-50% of T2DM patients developed diabetes [28,29]. The presence of both HF and T2DM has been shown to have a negative synergistic effect [30].

4. SGLT2 Inhibitors Improve Cardiac Metabolism and Bioenergetics

SGLT2 inhibitors are thought to improve cardiac energy metabolism, and potentially, with improving energy utilization and promoting greater efficacy of energy and substrate efficiency, SGLT2 inhibitors may help to regulate cardiac function by improving function and efficiently improving an individual's ability to produce cardiac output [31,32]. Diabetes and/or heart failure have protein-glucose metabolism reductions, including decreased regulatory function of metabolic flexibility in glucose and fatty acid use for ATP production [31,33]. The dependence on the use of NEFA to produce ATP may inadvertently push free fatty acid intermediates, which can accumulate and cause lip toxicity, reduce calcium accumulation inside the sarcoplasmic reticulum through diastolic dysfunction, Levitra release rates [33]β Hydroxybutyric acid production is slightly increased by SGLT2 inhibitors, and thus it is surmised that β Hydroxybutyric acid is a more efferent myocardial fuel source for those with T1D [31,34]. In addition to being used to increase the production of glucagon, ketones have been theorized to also utilize a decrease or suppression of the production or excretion of ketones through the renal route. The premise of the theory is that the 'super fuel' (as described above) produced by the kidney via β Hydroxybutyric acid increases the oxidation rate of glucose compared to NEFA and glucose, as well as providing a basal metabolic substrate for the productivity process of the heart through β Hydroxybutyric acid via the means of the failing heart [35]. There are currently very few strong data sources to provide evidence for this proposed theory. Nevertheless, a number of preliminary investigations on pigs after the cessation of a heart attack have provided some evidence in support of the proposed theory by demonstrating that the increase in Myocardial Ketone Usage, and a decrease in Myocardial Glucose Usage and Lactate Production [36]. In addition, the researchers opine that the increase in β-Hydroxybutyrate (βOHB) levels as a result of additional SGLT2 Inhibitors may be inhibiting Histone Deacetylase and blocking Transcriptional Networks within the Heart involved in Muscle Growth and Hypertrophy, and that an inhibition of βOHB Oxidation would result in an increase in glucose-derived Acetyl-CoA Oxidation, which in turn would improve myocardial metabolic pathways. Additionally, a reduction in Acetyl-CoA production could prevent Hyperacetylation/ Hyperacetylation of the Mitochondrial Enzymes, and beneficially affect Mitochondrial Energy Generation [40]. Another elegant, Untargeted Metabolomic Investigation, suggested that the SGLT2 Inhibitor would promote the breakdown of Intermediates of Branched Chain Amino Acids (BCAA) into alternative fuel sources for a non-functioning myocardium. Impaired BCAA breakdown has previously been described in Heart Failure; therefore, it has been postulated that impaired BCAA usage could be contributing to unwanted energy metabolism changes in the myocardium [37]. Thus, the above-mentioned aforementioned findings are very interesting, but while there is evidence supporting these ideas, to date there has not been sufficient evidence to establish a direct relationship between myocardial energetic pathways and the beneficial effects of SGLT2 Inhibition [38].

5. SGLT2 Inhibitor Used in Chronic Kidney Disease

Chronic kidney disease (CKD) can be diagnosed if certain criteria last for over three months; these criteria are: eGFR < 60 mL/min/1.73 m2 or kidney damage markers (of either structural or functional nature; one or several): albuminuria (urine excretion rate of albumin ≥ 30 mg/24 h; urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g [≥ 3 mg/mmol]), abnormalities in urine, disorders of renal tubules, and both pathological and structural changes in kidneys [39,40]. CKD is a widespread disorder that substantially contributes to the risk of cardiovascular complications, end-stage renal disease (ESRD), and death [39,40]. Data from 2021 suggest that the CKD prevalence in the USA is 15% (around 37 million adults), and the disease is more prevalent among the elderly (population aged 65 years or more) as opposed to the younger ones and in the non-Hispanic Black group as compared to the non-Hispanic White or Asian group [41]. CKD often goes unnoticed and not only is very little awareness from both the patients and doctors' side. In the ADD-CKD analysis of adults with type 2 diabetes (T2D), only 22% of patients with stage 3–5 CKD were recognized by their primary care physician as having CKD [42]. This fraction went up with the worsening of CKD stage, from 18% for stage

3, through 53% for stage 4, to 59% for stage 5 CKD [4]. More less the same is the case with both parts of CKD (i.e., eGFR < 60 mL/min/1.73 m2 and UACR ≥ 30 mg/g) being viewed as separate independent risk factors for CKD progression, development of ESKD and CVD as well as death [43,44]. There is still a huge gap in the market for more efficacious treatments for chronic kidney disease (CKD) that will not only slow down the progression of the disease but also prevent the development of end-stage kidney disease (ESKD) and cardiovascular diseases (CVD) including heart failure (HF) as well as prolong the life of CKD patients. In the past two decades, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been the only drug classes recommended for patients with CKD and hypertension, whether they have Type 2 diabetes (T2D) or not [40]. In the RENAAL (losartan) [45] and IDNT (irbesartan) [46] studies involving diabetic patients with nephropathy, both ARBs have been reported to reduce the risk of the composite renal endpoint (i.e., serum creatinine doubling, ESKD, or all-cause mortality) by 16% and 20%, respectively, as compared to the placebo group. Likewise, ACE inhibitors have been found to lower the probability of CKD progression among patients with diabetes as well as those without diabetes when compared to placebo treatment [47,48,49,50]. Further investigation on the combined effects of ACE inhibitor and ARB or using renin inhibitors has not yielded any additional benefits regarding the slowing of CKD progression or the trials were abruptly stopped due to the severe adverse effects (acute kidney injury, renal dysfunction, stroke, and/or hyperkalemia) [51,52,53]. Lately, researchers have conducted large, randomized, placebo-controlled trials to assess the cardiovascular safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in type 2 diabetes patients. The SGLT2 inhibitors not only cut down the chances of experiencing cardiovascular events dramatically, but they also minimized the chances of renal outcomes that are clinically meaningful, i.e., sustained loss of kidney function, eGFR decline, progression to or worsening of albuminuria, new ESKD, death from renal causes, and/or a renal composite outcome, when compared with placebo. Thus, SGLT2 inhibitors are considered to be the safer medicines for treating renal diseases, especially in the case of diabetic patients, who are more prone to develop kidney diseases, [54,55,56,57]. Nevertheless, the aforementioned studies were not explicitly aimed at evaluating the treatment advantages of CKD patients; only 7–26% of the total participants' eGFR was less than 60 mL/min/1.73 m2 [54,55,56,57]. Afterward, the precise kidney outcome trials revealed a significant reduction in the CKD risk that was associated with SGLT2 in combination with canagliflozin in CREDENCE [58] and dapagliflozin in DAPA-CKD [59] for both diabetic and nondiabetic kidney disease patients. Moreover, the FIDELIO-DKD trial focusing on the renal and cardiovascular effects of the MRA finer none over a long period of time reported less advancement of CKD in patients with diabetes-inked renal disease [60].

CONCLUSION

SGLT2 inhibitors are some of the key advances in modern pharmacotherapy, initially developed for glycemic control in T2DM but later recognized for their wide therapeutic benefits beyond diabetes. These agents, by inhibiting renal glucose reabsorption in the proximal tubules, provide effective glucose-lowering without dependence on insulin and with additional advantages such as weight reduction and low risk of hypoglycemia. Importantly, the cumulative clinical evidence has demonstrated substantial cardioprotective and Reno protective benefits associated with their use: a decrease in hospitalization for heart failure, a retardation of the course of chronic kidney disease, and an overall reduction in adverse cardiovascular events even in nondiabetic subjects. These offer other benefits than pure modifications of disease. With proper patient selection and monitoring, these agents can minimize certain safety concerns, including genital infections and rare reports of euglycemic ketoacidosis. On the whole, SGLT2 inhibitors have transformed the management paradigm of diabetes, heart failure, and chronic kidney disease toward integrated cardio-renal-metabolic care and underlined their expanding role in clinical practice.

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