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Systematic Review Article

SGLT 2 Inhibitors: Mechanisms, Clinical Applications, and Future Directions

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Abstract:

Due to the progressive and painful nature of type 2 diabetes (T2D), treatment may require periodic evaluation of patients, intensifying glucose-lowering therapy when glycaemic targets are not achieved and testing new methods. Among the newer classes of glucose-lowering drugs, sodium-glucose cotransporter 2 inhibitors (SGLT2is), which increase urinary glucose excretion to reduce hyperglycaemia, have made an impressive entry into the T2D treatment arsenal. Given their unique insulin-independent mode of action and favourable efficacy-adverse effect profiles, and their apparent benefits on cardiovascular-renal outcomes in intermediate-high-risk T2D patients, which have led to the updating of guidelines and product monographs, the role of this drug class in multidrug regimens is promising. However, despite much speculation based on pharmacokinetic and pharmacodynamic properties, physiological rationale and potential synergism, the glycaemic and pleiotropic effects of these agents when combined with other classes of glucose-lowering drugs remain largely under-researched. Therefore, this review discusses the mechanisms, clinical applications and future therapeutic role of SGLT2 inhibitors with a review of the literature.

1. Introduction

Despite the remarkable advances in the treatment of type 2 diabetes, its prevalence continues to increase. The aberrant activation of hepatic gluconeogenesis and reduced secretion of pancreatic insulin underlie the development of hyperglycemia, which can further exacerbate comorbid conditions leading to decreased vascular function, hypertension, hyperfiltration, and a proinflammatory state causing organ damage [1,2]. The sodium-glucose linked transporter 2 mediates almost 90% of glucose reabsorption in the proximal tubule of the kidney. Inhibition of this transporter results in glucosuria and lower postprandial hyperglycemia. Inhibitors of this transporter significantly reduce cardiovascular and major renal adverse events and ischemic limb events. This text discusses the modes of action, adverse events, and future directions for treating diabetes with these inhibitors [3,4].

The diabetes landscape is becoming very competitive, challenging drug manufacturers and researchers to provide better oral medications for treating type 2 diabetes. An old paradigm that remains important in treating diabetes is to alleviate hyperglycemia and glucosuria. Based on this premise, the design of competitive and potent inhibitors that also reduce weight and lower glucose immediately after eating is desirable. These inhibitors can be used as monotherapies to provide good glucose lowering, as well as in combination with oral anti-diabetic medications that do not increase blood glucose or weight [5]. Finally, these inhibitors can be used in combination with oral anti-diabetic medications that would increase blood glucose if they did not accelerate glucose excretion. The fate of this promising class of small molecule medications lies completely in the hands of the drug manufacturers and the incentives they can provide to the medical community [6].

1.1. Background and Significance

Traditionally, diabetes treatment has been dominated by either exogenous insulin or drugs that increase endogenous insulin secretion while reducing insulin resistance. In recent decades, weekly injectable medications and new oral formulations of older medications have entered the market. Among them, sodium glucose co-transporter-2 inhibitors are a new class of drugs that have the additional advantage of weight reduction, in addition to reducing glucose. Efforts to

understand the role of SGLTs and the development of their inhibitors have a long history in relation to diabetes, kidney diseases, and other systemic complications associated with diabetes [7, 8]. SGLT2 inhibitors have shown significant progress in the treatment of type 2 diabetes mellitus. SGLT2 inhibitors are the latest addition of oral antidiabetic agents with a unique mechanism of action, i.e., insulin independent, related to glycaemic control, as well as having potential cardiovascular benefits with weight loss, especially in the obese population. Given their multiple benefits, their efficacy as antidiabetic drugs to control HbA1c and the likelihood of severe hypoglycemia, it is important to understand the mechanism of action of the SGLT2 inhibitors and kidney and gastrointestinal physiology related to glucose metabolism and its role in body weight. Understanding these mechanisms will help clinicians incorporate these drugs into their medical algorithms designed to decrease microvascular and macrovascular diabetes complications [9, 10].

1.2. Scope of the Work

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, a relatively new class of oral anti-diabetic drugs, reduce hyperglycemia by inhibiting glucose reabsorption from the kidney tubules and thereby increasing glucose excretion. Mechanistic insight, clinical applications, and future directions of SGLT2 inhibitors are discussed based on current pharmacological understanding [11]. This preliminary essay aims to explain the existing understanding and provide a wider perspective, with this precise scope, to be clinically useful for potential applications. The focus will be on describing the application and not the underlying processes [12,13]. These necessarily require preventive awareness as well as distribution and sharing of the available data. In addition to the pharmaceutical perspective, the intended last part of this essay looks at recent advances in the directions desirable for future research in this area. We will specifically describe clinical applications and provide safety profiles that make a chapter on the use of obstructive FDE when submitting follow-up counselling and necessary additional work. We further discuss exciting findings and, through the elucidation of the potential mechanisms, can find a useful expression of these side effects [14]. If proven, it can be used in wider therapeutic methods. While taking these precautions into consideration, the side effects associated with each drug are very important from a clinical point of view. Regarding the scope of this essay, the use of these drugs became essential in the wake of the big data that has emerged so far or is likely to emerge soon. Therefore, the evidence base and clinical experience of these drugs are widely used as a guide for the information that will be covered in the essay [15].

2. Mechanisms of Action

Sodium glucose-linked transporter 2 (SGLT2) transporters are responsible for reabsorbing glucose filtered through the glomeruli. Reabsorption of 90%–95% of filtered glucose occurs via the SGLT2 protein in the early proximal convoluted tubule (PCT), while the SGLT1 transporter is present in the S3 segment of the PCT and absorbs the remaining glucose. In diabetes, or in the presence of other SGLT2 inhibitors, loss of renal glucose handling enables glucose to be reabsorbed by the dentate gyrus (DG) of the kidney. This, in turn, allows submaximal activity of SGLT1 in the late PCT, thus also increasing glucose absorption in this segment [11, 16]. Although the exact significance of SGLT1 transporters in diabetic conditions is uncertain, the relevance is primarily of interest for long-term type 2 diabetes (T2D) treatments, in which SGLT2 inhibitors will also provide added context for treating obesity earlier. The novelty of their underlying mechanism of action, as well as their ability to potentially target a component of the vasoconstrictor response, further highlights the innovative nature of the SGLT2 inhibitors. These inhibitors have garnered immense attention and interest in the medical research community due to their potential to revolutionize the treatment of diabetes [14, 17]. By specifically targeting the SGLT2 transporters, these inhibitors offer a unique approach to managing blood glucose levels and reducing the risk of complications associated with diabetes. Furthermore, the potential of SGLT2 inhibitors to address obesity earlier in the disease progression is a promising aspect. Obesity is strongly correlated with the development of type 2 diabetes, and by targeting both conditions simultaneously, these inhibitors have the potential to provide comprehensive and effective treatment options for patients. The innovative nature of SGLT2 inhibitors extends beyond their glucose-lowering effects. They have also shown potential in modulating the vasoconstrictor response, a physiological mechanism that narrows blood vessels and increases blood pressure. By targeting a component of this response, SGLT2 inhibitors may have additional cardiovascular benefits that further contribute to their therapeutic potential [18]. In summary, SGLT2 inhibitors represent a noteworthy advancement in the field of diabetes treatment. Their unique mechanism of action, ability to target both diabetes and obesity, and potential cardiovascular benefits make them a promising option for patients

and researchers alike. As further studies and clinical trials continue to explore the full extent of their benefits and effectiveness, the future of SGLT2 inhibitors remains bright [11, 14].

Physiologically, SGLT2 inhibitors are unique due to their mechanism of enhancing urinary glucose excretion (UGE). SGLT2 inhibitors directly alter the adherence of the luminal membrane to the submembrane cytoskeleton specifically in the PCT S1 segment, thus resulting in a reversible outplacement of the luminal membrane [19]. This membrane shedding leads to an increase in SGLT2 protein excretion, such that 50% of the original SGLT2 protein at baseline will be present in the lumen of the tubule at equilibrium. SGLT2 protein excretion is able to occur because the glucose produced as a secondary effect will promote glucosuria directly adhering to the remaining luminal SGLT2 protein. The final urinary glucose concentration achieved is about 50–70 mm for normal urine flow rates. Following the approval of SGLT2 inhibitors for the treatment of T2D, many additional physiological and metabolic improvements have been described in human subjects as secondary benefits of glucosuria [20, 21].

2.1. Overview of SGLT 2 Transporters

Sodium-glucose co-transporters 2 (SGLT2) are a set of transporters that primarily facilitate the movement of glucose and sodium from the proximal tubule to the systemic blood circulation. SGLT2 transporters are present in the brush border membrane of the kidney and are involved in the reabsorption of glucose from the urine back into the blood. Normally, glucose is filtered and excreted by the kidney, but approximately 99% of glucose is reabsorbed back into the blood [11. 22]. In humans without diabetes, the glucose reabsorption in the renal tubules is mainly performed by SGLT2, while only a small portion of glucose is reabsorbed by SGLT1. In general, SGLTs actively transport sodium, which then drives the glucose molecules against their concentration gradient into the system. By varying the concentration of sodium, glucose absorption rates are allosterically increased. This reabsorption of glucose ultimately raises the serum glucose concentration; however, pathological SGLT2 activity can result in the survival of more glucose in the urine, leading to higher excretion of glucose. The SGLT2 transport mechanism is dependent on the sodium gradient and ATP hydrolysis and is regulated by hormonal action to a certain extent [23]. There is a close interaction between SGLT2 and the actions of insulin, which can directly inhibit SGLT2 sodium-glucose transfer rather than mediation by signalling pathways. There is no definitive result on the modulation between insulin action and SGLT2, as there are differences in results based on studies. Inhibition of SGLT2 by its inhibitors decreases glucose reabsorption in the kidney, leading to glucose excretion in the urine [24].

2.2. Pharmacodynamics of SGLT 2 Inhibitors

The pharmacodynamics of SGLT2 inhibitors relate to their mode of action. They inhibit the SGLT2 co-transporter in the early part of the proximal tubule, resulting in a decline of renal glucose reabsorption and increased urinary glucose excretion. This leads to a reduced renal threshold for glucose and an increase in glycosuria. SGLT2 inhibitors block approximately one third of glucose excretion and increase urinary glucose excretion to peak with doses ranging from 25 to 400 mg within only 1 to 2 weeks after initiation. The urinary glucose excretion remains increased for up to at least 24 hours, thereby also reducing the postprandial glucose. The loss of glucose from the body is compensated for by an equimolar increase in gluconeogenesis and, to a lesser extent, by an increase in glycogenolysis, thereby providing an internal glucose source [19, 24, 25].

SGLT2 inhibitors exert an antihyperglycemic effect in patients with type 2 diabetes, with average placebo-subtracted HbA1c reductions at 3 months ranging from 0.6% to 1.4%. Their action is insulin-independent, and they are associated with weight loss of up to 3 kg. In addition, they decrease blood pressure and reduce uric acid, contributing to additional cardiovascular and metabolic benefits. The antihyperglycemic effects of SGLT2 inhibitors in patients with type 2 diabetes are similar for different levels of HbA1c and eGFR, although they decline slowly from an eGFR of 45 mL/min/1.73 m² because of the reduction in renal glucose excretion. Their urinary glucose excretion has been associated with plasma reductions of phosphate and albuminuria. Overall, SGLT2 inhibitor-induced urinary glucose excretion supports clinical effectiveness, but its magnitude is variable. Magnitude and duration of urinary glucose excretion depend on recommendations for SGLT2 inhibitors dose and glomerular hyperfiltration [24, 26].

3. Clinical Applications

SGLT2 inhibitors have become a mainstay in the management of patients with type 2 diabetes mellitus (T2D) because of their efficacy and seemingly long-term safety profile. They complement the use of other agents in the management of diabetes because of their multiple actions, including reductions in

body weight and blood pressure [27, 28]. Despite their current role and significant advantages, however, evidence is starting to evolve around practical questions regarding such agents. SGLT2 inhibitors are now extensively used for patients with T2D in whom glycemia remains uncontrolled when agents acting on the incretin system fail to provide additional glucose-lowering efficacy. Clinical trials have also evolved wherein SGLT2 inhibitors are being used alongside GLP-1 receptor agonists. It is also slowly becoming clearer that the metabolic risks and advantages of a newly diagnosed patient can guide the initiation of treatment [29].

Importantly, when selecting treatments independently of glycemia/hyperglycemia, recent guidelines on the management of T2D clearly show a preference for initiating with an SGLT2 inhibitor with proven cardiovascular and renal safety benefits. This reflects two major dimensions: the efficacy of the agents in their targets (with respect to cardiovascular effects and renal effects), and the evidence of the agents being non-harmful. Currently available drugs in the US that are recommended as first-line agents include ***empagliflozin*** and ***canagliflozin***. Other potential first-line agents listed include ***liraglutide*** among other GLP-1 receptor agonist class drugs [30-32]. In addition to being a first-line agent in this setting, these agents are also recommended as add-on therapy to metformin, particularly for those with pre-existing atherosclerotic cardiovascular disease risk and heart failure. Liraglutide, semaglutide, and dulaglutide are also among the recommended agents to be used as add-on therapy when an SGLT2 inhibitor is not obtained [33].

3.1. Treatment of Type 2 Diabetes Mellitus

Treatment of Type 2 Diabetes Mellitus with Sodium-Glucose Co-Transporter 2 Inhibitors. Beyond glycemic control, SGLT2 inhibitors have cardioprotective and nephroprotective effects and treat obesity. Since results from a major trial were published in 2015, an SGLT2 inhibitor has been considered a key component of treatment if a patient with T2DM has atherosclerotic cardiovascular disease, heart failure, renal disease, and obesity in the presence of indications such as tolerable renal function, without end-stage renal disease. Moreover, because the effects of SGLT2 inhibitors still remain after HbA1c has plateaued, no dose escalation of SGLT2 inhibitors is recommended or indicated solely to improve glycemic control if a patient does not achieve the HbA1c target [34]. This concept is unique to SGLT2 inhibitors. Indeed, the treatment of patients with T2DM has shifted from just glucose control to multi-drug usage guided by comprehensive specific needs (cardiovascular disease, heart failure, and renal disease) and comorbidities (obesity) on a per-patient basis [35].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors lower plasma glucose levels with a glucose-independent effect through the excretion of glucose in urine. To promote urinary glucose excretion, SGLT2 reduces the reabsorption of filtered glucose in the renal proximal tubules. SGLT2 inhibitors improve glucose control by lowering both fasting plasma glucose and postprandial glucose. There is an inverse linear correlation between SGLT2 inhibitor-mediated increase in urinary glucose excretion and decrease in hyperglycemia. SGLT2 inhibitors affect the glucose level without initial dose titration and weight gain. The most consistent effect of SGLT2 inhibitors is a gradual reduction in HbA1c level. In clinical trials, the HbA1c-lowering effect has been found to be approximately 0.5 to 0.7% from the baseline. The maximum HbA1c-lowering effect is at four to 12 weeks after initiation and remains until the end of treatment. In all, SGLT2 inhibitors proved to be clinically effective for improving glycemic control based on results of controlled trials and comparative trials for short- and long-term treatment [36, 37].

3.2. Cardiovascular and Renal Benefits

Cardiovascular and Renal Benefits. The cardiovascular protective effect of SGLT2 inhibitors has been presented in many large-scale clinical trials. These studies have consistently provided evidence of reduced risk of major adverse cardiovascular events and the progression of chronic kidney disease in patients with type 2 diabetes. Translating to clinical practice, these benefits are thought to be irrespective of hypoglycaemics effects and independent of baseline HbA1c or blood [38]. These agents offer a benefit cap dependent on circulatory conditions such as cholesterol; however, the extent to which the benefits could be maximized remains to be clarified. Mechanisms behind the cardiovascular protective effect of SGLT2 inhibitors are believed to be related to various factors and advantages, such as arterial stiffness regression and reduction of left ventricular myocardial fibrosis. Hemodynamically, SGLT2 inhibitors can reduce pre- and afterload, whereas possible renal benefits regarding reductions in hyperfiltration and albuminuria manifest primarily as a decrease in inflammatory processes. Further investigations will facilitate a proactive approach in favourable patient selections for whom cardiovascular or renal benefits still have the possibility to be maximized [39, 40].

The reduced risk of heart failure development and disease progression in the treatment of existing cardiac failure of these agents has been observed. Stellar landmark trials have shown promising results

within relatively short times of initiating the trials. These cardiovascular benefits were validated by trials which demonstrated positive outcomes within a patient population with lower cardiovascular risks. These trials also demonstrated improvements in terms of renal protective effects [37, 41]. These trials serve as solid evidence for the efficacy of SGLT2 inhibitors across a broad spectrum of patients and their cardiovascular risks. Interestingly, recent experimental studies have explored the mechanisms behind the cardiovascular and renal benefits of SGLT2 inhibitors. Current knowledge supports the use of cardiovascular outcome trials and renal outcome trials as a guide to selecting patients most likely to benefit from SGLT2 inhibitors in terms of cardiovascular disease. In terms of autopsy investigations, the net beneficial cardiovascular effects of SGLT2 inhibitors have been recently researched. In patients with type 2 diabetes mellitus, early onset coronary atherosclerosis was associated with vulnerable plaque, myocardial infarction, and microvascular disease [42]

4. Safety and Adverse Effects

The safety profile of SGLT2 inhibitors is a fundamental determinant of treatment allocation in clinical settings. The main side effects of SGLT2 inhibitors are related to glucosuria, mainly including urinary tract infections and genital mycotic infections; in both cases, the possibility of a relevant concentration-dependent proliferative effect of glucose deprivation in bacterial or fungal pathogens has been suggested. Besides these large categories of side effects, case reports exist for other, less common side effects. The two most serious but rare events associated with it are diabetic ketoacidosis and acute kidney injury. It is important for the clinician to be aware of these possible side effects and adverse events in the patients on these drugs to develop strategies to minimize the risk of occurrence and increase the possibility of successful management or favourable outcome if it occurs [43, 44].

Though no definitive scale is available to predict who may encounter these events, a certain amount of risk stratification can be achieved on the basis of existing literature mainly drawn from population response studies. Type 1 diabetes patients may have a higher risk of developing euglycemic DKA. In real-world studies of observational post-marketing surveillance, no increase in serious events has yet been demonstrated. In major trials as well, nephrological adverse events have been rare [45, 46]. Physiological prudence, especially in terms of past and ongoing renal function in the patients, is thus warranted for initiation and continued therapy, with cautious monitoring according to labelling and individual patient characteristics. At the same time, these drugs may require caution when analysed in terms of drug-nutrient interactions [47]. Sufficient information must be provided to the patient for the development of complete and informed consent, centred on shared decision-making processes. It is unknown what proportion of patients might be deterred from the use of SGLT2 inhibitors for fear of such risks [19, 48, 49].

5. Future Directions and Emerging Research

Novel combinations with other pharmacological agents: albeit SGLT2 inhibitors have shown broad therapeutic effects in various disease states, new combinations with other drugs go beyond their insufficient activity. The combinations act on other disease pathways with the goals of decreasing the necessary dose of each drug to avoid some side effects and, in some cases, to decrease the risk of the occurrence of resistance to some other pharmacological agents. We need to perform combined treatment strategies under pre-specified conditions that allow for the achievement of additive or synergistic effects [50]. Metabolomic and other molecular markers may be useful for the implementation of these disease-modifying monotherapy combination studies. Many possibilities can be explored, especially focusing on CVD and comorbidities. Prevention: Given the beneficial effects of SGLT2i, novel trials should be designed to evaluate the long-term efficacy of these drugs in asymptomatic healthy individuals with risk factor bundle metabolic syndrome, pre-diabetes, early markers of macro- and/or micro-angiopathy, etc. in order to decrease or delay the appearance of overt disease [51].

Tailored SGLT2i treatments: Nowadays, there is a growing interest in pharmacologic therapies that provide a multiplicity of effects by targeting diverse yet related pathophysiological and mechanistic targets. A first approach has been described for combining SGLT2i and liraglutide in patients with T2D to assess synergism in controlling T2D and prevent or slow down CV diseases. Further studies might offer new possibilities to explore tailored cardiovascular, or even diabetogenic, benefits of these pharmacologic agents. Accordingly, an analysis utilizing historical guidelines could be provided. Alternative scenarios: Tailoring anti-diabetic treatments according to their hemodynamic actions and preliminary beneficial effects on the heart could be valuable in patients with HF, at any stage, and in patients at risk of developing HF or CVD. Several ongoing trials with a combined clinical end, as well as some studies combining

SGLT2i and other hypoglycaemics agents on the beta cell, for instance. Future research should focus on other important populations according to CVDRS or CVDGP other than T2D for comprehensive approaches. So, randomized controlled trials, a non-randomized intervention, and prevention study, registry-based studies with sex-specific inclusion, follow-up and analysis, and real-world studies are required. Desirable research infrastructures, research collaborations, consortia, and meta-analyses have been suggested in the previous discussion. Participants of the consensus areas discussed this topic but have come to the conclusion that they are beyond the scope of this document and will be discussed in future similar works.

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