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Mechanisms and Therapeutic Potential of SGLT2 Inhibitors

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Abstract

Introduction and Purpose. Epidemiological data indicate that the global prevalence of diabetes is projected to reach 784 million by 2045. This trend is closely associated with an increase in chronic kidney disease (CKD) and heart failure (HF), which remain the primary causes of mortality in this population. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins, were originally developed as hypoglycemic agents but have demonstrated significant pleiotropic benefits. The purpose of this study is to analyze the multidimensional mechanisms of SGLT2 inhibitors and evaluate their clinical impact on type 2 diabetes, heart failure, and renal protection.

Brief Description of the State of Knowledge. Gliflozins function through an insulin-independent mechanism by blocking glucose reabsorption in the proximal renal tubules, leading to glycosuria. This process effectively lowers HbA1c levels without inducing hypoglycemia. Beyond glycemic control, SGLT2 inhibitors activate tubuloglomerular feedback, leading to afferent arteriolar vasoconstriction and a reduction in intraglomerular pressure. These drugs provide significant cardioprotection by reducing cardiac preload and afterload and improving myocardial energy efficiency through ketone body utilization. Clinical trials confirmed that gliflozins reduce hospitalizations for HF. Furthermore, they contribute to weight loss and blood pressure reduction. While generally safe, they are associated with risks of urogenital infections and rare complications such as euglycemic ketoacidosis.

Summary. SGLT2 inhibitors represent a breakthrough interdisciplinary therapy. Their potential efficacy in reducing cardiovascular mortality and renal failure progression is

observed in both diabetic and non-diabetic patients. Given their organ-protective properties, gliflozins have become a cornerstone in modern diabetology, cardiology, and nephrology.

Key words: SGLT2 Inhibitors, Diabetes Mellitus Type 2, Heart Failure, Diabetic Nephropathies.

1. Introduction

Epidemiological projections suggest that the global prevalence of diabetes will continue to rise, reaching up to 784 million people by 2045. The disease is often accompanied by chronic kidney disease (CKD) and a heightened risk of cardiovascular complications, including heart failure. It is important to note that cardiovascular complications remain the leading cause of death among these patients. These data suggest that the number of individuals requiring treatment for diabetes, chronic kidney disease, and heart failure is expected to increase [1,2].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally introduced as hypoglycemic agents for type 2 diabetes, have demonstrated high efficacy in reducing blood glucose levels and glycated hemoglobin (HbA1c) [3]. However, clinical data have shown that their action profile is more extensive. SGLT2 inhibitors significantly reduce the risk of hospitalization for heart failure and serve as a cornerstone of CKD therapy by limiting progression to end-stage renal disease. Furthermore, specific agents within this class correlate with a reduced risk of acute kidney injury. Notably, these nephro- and cardioprotective effects are observed even in patients without a diagnosis of diabetes [3,4].

The high efficacy of gliflozins in treating type 2 diabetes, heart failure, and CKD has been confirmed by the guidelines of leading cardiological, diabetological, and nephrological societies [2,5,6]. This diverse range of clinical applications provided the basis for the analysis of SGLT2 inhibitor mechanisms and the evaluation of their impact on the aforementioned conditions conducted in this study.

2. The pleiotropic mechanism of action of SGLT2 inhibitors (flozins)

The kidneys are remarkable organs that perform many functions essential to the organism's functioning. One of its functions is to play a role in glucose metabolism and maintain proper glucose levels. Approximately 90 percent of the kidney's ability to reabsorb glucose is attributed to SGLT2 expression [3]. The kidneys are the primary site of SGLT2 expression, particularly in the apical membrane of the S1 and S2 segments of the proximal tubule [7]. Through glucose transporter-2, intracellularly accumulated glucose exits the tubular cells and moves to the interstitial fluid and the peritubular capillary. SGLT2, thanks to its effects, is a desirable therapeutic target to decrease the amount of glucose that is reabsorbed into the bloodstream from urine [3]. Nearly all of the glucose filtered by the renal glomerulus is subsequently reabsorbed in healthy individuals. However, glucose reabsorption capacity decreases and urine glucose excretion increases when plasma glucose levels are beyond a threshold (about 180 mg/dL or 10 mmol/L)[3].

When patients without type 2 diabetes have normal plasma glucose levels, SGLT2 inhibitors cause a persistent urine glucose excretion of 40 to 80 g/d. Urinary glucose excretion rises when plasma glucose concentrations increase in T2DM patients taking SGLT2 inhibitors [8]. Reabsorption of sodium and glucose is decreased when sodium-glucose cotransporter 2 (SGLT2) is inhibited. Hypoglycemia following SGLT2 inhibitor medication is believed to be prevented by a compensatory increase in glucose reabsorption by SGLT1 [8, 9]. In addition to affecting blood glucose levels, SGLT2 inhibitors influence other important factors, including hypertension. It is supposed that these substances reduce intraglomerular pressure by activating tubuloglomerular feedback.The mechanism of action is related to the concentration of salts in the tubular fluid within the macula densa. Apical Na^+-K^+-$2Cl^-$ cotransporters (NKCC2) in the macula densa detect the concentration of substances in the tubular lumen, which leads to the release of ATP from the basolateral membrane. The amount of ATP released is proportional to the concentration of the solute. ATP binds to or cleaves P2 purinergic receptors on afferent arterioles, releasing adenosine. ATP's effect on P2 purinergic receptors and adenosine's action on A1 receptors cause afferent arteriolar vasoconstriction. Adenosine also acts on juxtaglomerular cells by reducing renin secretion and by decreasing the constriction of efferent arterioles, which is mediated by the renin-angiotensin-aldosterone system. Increased afferent arterial tone and reduced efferent arterial tone lower intraglomerular pressure. These processes ultimately lead to a decrease in blood pressure [3,4,10].

3. Clinical applications

3.1. Treatment of type 2 diabetes.

Type 2 diabetes is a combination of both genetic and environmental factors [11] The goal of treatment is to prevent or delay the onset of complications, as well as to prevent loss of quality of life. Patient engagement is crucial to the success of treatment [12].

In recent years, sodium-glucose cotransporter 2 inhibitors (SGLT2i), also known as gliflozins, have been used in the treatment of type 2 diabetes [11]. Clinical studies have indicated that they effectively lower blood glucose levels and glycated hemoglobin (HbA1c) by 0.5 to 0.9% (5–9 mmol/mol) after 12 months of therapy in patients with type 2 diabetes, without causing hypoglycemia [3,11].

In addition, gliflozins protect against hospitalization for heart failure (HF), reduce the risk of cardiovascular complications, and slow the progression of chronic kidney disease. Their side effects are minimal, including an increased risk of urinary tract and genital infections [3,13]. The development of SGLT2i was prompted by the identification of phlorizin, a glucoside found in the root bark of fruit trees that blocks sugar transport in the small intestine and kidneys, among other places. Studies conducted on diabetic rats confirmed that phlorizin, which induces glycosuria, is responsible for the normalization of plasma glucose levels and the return of insulin sensitivity, without hypoglycemia [3].

These medications function through an insulin-independent mechanism, regulating glycemia by preventing the reabsorption of filtered glucose in the kidneys [13]. Sodium-glucose cotransporter 2, situated in the proximal renal tubule, is essential for glucose reabsorption, facilitating the transport of glucose from the renal tubule lumen to the epithelial cells that line the tubule. SGLT2 inhibitors interfere with the function of this protein, reducing blood glucose levels [11].

The glucocorticoid effect results in additional advantageous outcomes, including clinically meaningful decreases in systolic blood pressure and weight reduction [11,13]. According to one clinical trial, empagliflozin treatment reduced body fat, BMI, and visceral fat [14].

Data from meta-analyses of clinical trials confirm weight loss in patients treated with empagliflozin. The average weight loss was approximately 2 kilograms. Glycosuria, which forces negative energy balance and water loss through osmotic diuresis, plays a role here. [11] Inhibiting SGLT2 induces changes in metabolic processes, increases glucagon release, and stimulates lipolysis and lipid oxidation. The body limits glucose utilization in favor of fatty acid and ketone body metabolism, which promotes fat loss [11,13].

Additionally, changes in substrate availability, such as decreased amino acid levels, affect mitochondrial morphology, which transitions from a fission state to a stable fusion state [13].

3.2. Use in heart failure

SGLT2 inhibitors have also been used in cardiac patients. Compared to the general population, patients with T2DM are at almost twice the risk of developing HF. Their coexistence, in turn, worsens the prognosis. Significant risk factors for developing HF in patients with T2DM include kidney disease, but also obesity, hypertension, retinopathy, higher NT-proBNP levels, and coronary artery disease. For every 1% increase in HbA1c, the incidence of HF increases by 8%-36% [15,16].

To reduce the risk of cardiovascular events, the use of SGLT2i was recommended in the 2019 European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) guidelines for patients with type 2 diabetes who have been diagnosed with cardiovascular disease or who are at high or very high cardiovascular risk. Gliflozin therapy has been a breakthrough in improving hospitalizations due to HF [16].

Studies have reported that gliflozins are effective in treating the medium- and long-term complications of T2DM. They contribute to reduced morbidity and mortality from cardiovascular causes, such as heart failure and vascular disease [14,16]. According to the CANVAS, DECLARE-TIMI 58, VERTIS-CV and EMPA-REG OUTCOME studies, hospitalizations for HF significantly decreased in patients treated with SGLT2i. Mortality also decreased, both from cardiovascular and all-cause causes (in the EMPA-REG and CANVAS studies) [16].

A number of mechanisms can be identified for gliflozins that play a role in protecting the circulatory system, one of which is the reduction of fatty tissue accumulation in the

myocardium. Additionally, this group of drugs reduces cardiac preload and afterload and lowers blood pressure. As a result of lowering plasma glucose levels, circulating ketones increase, which in turn leads to improved energy efficiency in the myocardium [13,16].

According to the available literature, the effectiveness of gliflozins in older and frail patients is comparable to that in younger individuals. The older population is particularly vulnerable to the adverse effects of hospitalization, such as an increased risk of infection and deterioration of cognitive and physical functions, leading to loss of independence. Therefore, the action of SGLT2i is particularly important in this group, significantly reducing the risk of hospitalization due to HF [17].

3.3. Use in kidney diseases

SGLT2 inhibitors, due to their primary site of action in the kidneys, constitute a group of substances with nephroprotective effects. The use of SGLT2 inhibitors leads to a reduction in GFR via tubuloglomerular feedback, resulting from the constriction of afferent arterioles and the potential dilation of efferent arterioles. This reduces the pressure in the glomerular capillaries. A decrease in GFR has far-reaching consequences. Lower glomerular filtration pressure reduces tubular transport activity, thereby decreasing the kidney's oxygen consumption [9].

In patients with diabetes, diabetic kidney disease is a common complication of the condition. SGLT2 inhibitors block the reabsorption of glucose in the proximal tubule, thereby lowering blood glucose levels without hypoglycemic effects [3,18]. High blood glucose levels have a significant impact on kidney function. In particular, they lead to inflammation and fibrosis of the glomeruli. Hyperglycemia leads to vascular damage through various mechanisms, including excessive production of reactive oxygen species in endothelial cells and protein glycation, activation of protein kinase C and Janus kinase (JAK)-signal transducer. When glomerular podocytes are exposed to these advanced glycation end products (AGEs), nuclear factor levels rise. KB (NF-κB)-associated increase of messenger RNA production for several proinflammatory mediators. AGEs attach to the receptor for AGE (RAGE) within podocytes and endothelial cells, causing inflammation through the nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 (NLRP3) inflammasome. When all of these expressions are combined, NF-κB and NLRP3 cause the interleukins (IL0, IL-1B, and IL-18.22) to be expressed and activated. AGEs also raise serum amyloid A

expression, which feeds the inflammatory cycle. Continuous proinflammatory mediator release, immune cell recruitment, and ultimately profibrotic factors are caused by the intracellular mediators' signaling [18].

According to preclinical research, SGLT2 inhibition may have an overall anti-fibrotic effect by reducing the synthesis of pro-inflammatory and -fibrotic mediators (TNFR1, IL-6, MMP7, and FN1), blunting the expression of harmful toll-like receptor-4 (TLR-4), and reducing the activation of nuclear factor kappa B (NF-κB) [3,7]. SGLT2 inhibitors reduces expression of smooth muscle collagen IV and α-actin, as well as increases expression of the protective proteins STAT1 and transforming growth factor β1, was also observed, which has a significant impact on the process of glomerular fibrosis [3]. Hyperfiltration is a consequence of the harmful effects of hyperglycemia on the kidneys. As such, it contributes to the progression of kidney disease. SGLT2 inhibitors reduce the reabsorption of substances excreted in primary urine, activate tubuloglomerular feedback, decrease intraglomerular pressure, and thereby reduce kidney damage caused by hyperfiltration [4]. Hyperfiltration can also lead to proteinuria, caused by damage to the glomerular filtration units. Persistent proteinuria can result in permanent kidney damage. Studies show that SGLT2 inhibitors have a nephroprotective effect in kidney diseases associated with proteinuria [8]. The benefits of SGLT2 inhibitors are not limited to people with diabetes. According to the study, sodium-glucose cotransporter 2 (SGLT2) inhibitors lower the risk of acute renal injury, hyperkalemia, and the progression of kidney disease in individuals with or without diabetes [10].

A rather interesting and important protective effect of SGLT2 inhibitors is the reduction in the use and delivery of energy substrates to the kidneys. The reabsorption of glucose in the proximal tubule is a process indirectly driven by the sodium-potassium pump, which consumes energy. Inhibition of the SGLT2 receptor leads to reduced energy consumption. It reduces renal medullary hypoxia and limits oxidative stress [3,4].

4. Safety profile

SGLT2 inhibitors demonstrate numerous clinical benefits. The most important benefits include reducing the risk of cardiovascular death and slowing the progression of chronic kidney disease [19,20]. They are also highly effective in reducing all-cause mortality. Therefore, these drugs are considered safe and widely used in diabetology, cardiology, and nephrology [21].

4.1. Standard Dosage of Drugs in This Class

Preparations such as dapagliflozin and canagliflozin are administered orally, regardless of meals. Patients typically take 10 mg of the drug once daily. Appropriate dosing of these drugs is clinically important. This is confirmed, among others, by the study by Heerspink HJL et al., which showed that an appropriately selected dose of dapagliflozin significantly reduces the risk of a composite endpoint, which included a sustained decline in eGFR by at least 50%, end-stage renal disease, or death from renal and cardiovascular causes [19,22].

4.2. Most Common Adverse Effects

The use of SGLT2 inhibitors is associated with the risk of adverse effects. These are primarily due to the mechanism of action of these drugs. The most common adverse effects include urogenital infections. This is a serious problem for patients, potentially reducing their quality of life. Urogenital infections result from the excretion of glucose in the urine, and glucose serves as a breeding ground for microorganisms normally found in these systems. Fungal infections are also more common in patients taking SGLT2 [20].

Another serious adverse effect is disturbances in water and electrolyte balance. This is a direct result of the induction of osmotic diuresis in patients taking SGLT2. This can lead to fluid loss and, consequently, dehydration [20,23].

SGLT2 has also been observed to have an effect on blood pressure due to the aforementioned natriuresis. Blood pressure may decrease in these patients, although this is rarely reported in clinical data. Additionally, at the beginning of SGLT2 therapy, patients may experience a transient decrease in eGFR of approximately 3–5 ml/min/1.73 m². However, these changes are reversible, and the long-term benefits of the drug's protective effect on the kidneys outweigh this side effect [23].

4.3. Rare Complications

Literature indicates that patients taking SGLT2 preparations may experience rare, but very serious, adverse reactions, including euglycemic ketoacidosis (EDKA). This life-threatening complication involves metabolic acidosis occurring at relatively low blood

glucose levels, <200 mg/dL [24]. Therefore, these patients are at risk of inadequate treatment by the medical team.

Hypoglycemia is also a rare complication. The risk of a hypoglycemic episode increases when SGLT2 inhibitors are co-administered with insulin secretagogues. Such drugs include sulfonylureas and insulin. In such situations, physicians should reduce the dose of the insulin secretagogue or insulin itself when combined with canagliflozin. It is worth noting, however, that the rate of hypoglycemia in patients taking SGLT2 is considered low, confirming the safety of the drugs we discussed [25,26]. Another rare phenomenon that has been observed is an increased risk of amputation, particularly of the lower limbs. However, this is likely a class-specific characteristic, not specific to canagliflozin [23].

4.4. Contraindications

Contraindications to the use of SGLT2 medications include hypersensitivity to any of the ingredients or diabetic ketoacidosis [27].

In patients hospitalized for surgery, treatment should be interrupted for a maximum of 3–4 days, depending on the type of procedure, among other things. The patient's current condition is also important when considering medication discontinuation before surgery. In individuals with a low BMI, long-term diabetes, or renal impairment (eGFR < 45 ml/min/1.73 m^2), the most conservative treatment is used, which involves discontinuing medication for 3–4 days before the procedure. This recommendation also applies to patients taking flosins and glucagon-like peptide-1 receptor agonists (GLP-1 RA) concomitantly. According to current knowledge, these medications may delay gastric emptying. This may potentially prolong the fasting state and enhance the ketogenic effect. Additionally, caution should be exercised in patients with a history of ketoacidosis [28].

Patients with renal impairment, whose creatinine clearance is <20 ml/min/1.73 m^2, deserve special attention, as SGLT2 therapy should not be initiated in such individuals [29]. Caution should also be exercised when using these medications in individuals over 75 years of age, as these individuals are at increased risk of fluid depletion. Such patients should be educated about maintaining adequate fluid intake [20,23].

Temporarily suspending SGLT2 therapy should also be considered in patients with complicated urinary tract infections due to their mechanism of action. Additionally,

canagliflozin should not be used in patients at high risk of amputation [23]. Furthermore, SGLT2 inhibitors are contraindicated in pregnant women. Animal studies have demonstrated reproductive toxicity, with the highest teratogenic risk believed to occur during the second and third trimesters of pregnancy [30].

4.5. Possible Interactions with Other Drugs

In clinical practice, patients are often combined with different types of medications to optimize treatment and achieve a better clinical outcome. This also applies to SGLT2 inhibitors, which can be combined with, among others, GLP-1 RAs. This combination is very beneficial, as it can significantly reduce the risk of major circulatory complications (MACE). It also reduces the likelihood of hospitalization for heart failure, and this effect is more pronounced compared to monotherapy [31].

Another positive example of combining medications is the use of empagliflozin or remogliflozin with metformin, as this combination allows for a better reduction in HbA1c levels than, for example, glimepiride monotherapy. This indicates better glycemic control in the long term [32,33]. Another combination used is a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sodium-glucose cotransporter type 2 (SGLT2) inhibitor. These represent a promising option for combination therapy in terms of safety and efficacy, as their mechanisms of action are complementary, and the interaction between these drugs is clinically imperceptible, although possible in pharmacological theory [34].

Furthermore, SGLT2 inhibitors used in patients undergoing chemotherapy or radiotherapy may potentially improve the prognosis of gastrointestinal cancer patients. This effect is significant because flosins do not cause significant side effects [35].

However, possible adverse interactions of flosins with other drugs should be considered. Due to the decrease in eGFR at the beginning of flosin treatment, they may enhance the nephrotoxic effects of other drugs [36]. In a study by David S. Gomes et al. Attention was also drawn to the growing problem of the co-occurrence of tuberculosis and diabetes. Treating patients with these diseases is difficult because one of the drugs, rifampicin, can potentially interact with other medications. Therefore, when rifampicin is used concurrently with canagliflozin, patient doses should be carefully adjusted. However, dapagliflozin, ertugliflozin,

and empagliflozin are considered safer alternatives. It is also recommended that patients undergo hematological monitoring during treatment with linezolid and dapagliflozin [37].

It is worth emphasizing that any possible interactions between flozins and other drugs are still under investigation. However, currently, SGLT2 inhibitors demonstrate a low probability of interactions with other drugs and are considered safe.

5. Summary

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, or gliflozins, represent a breakthrough in metabolic and cardiovascular therapy, extending significantly beyond their primary role as antidiabetic agents. As demonstrated, a key aspect of their efficacy is not only glycemic control (with an HbA1c reduction of 0.5–0.9%) but, above all, a multidimensional impact on the cardiovascular system and the kidneys. This broad spectrum of action is achievable through a relatively simple oral dosing regimen administered once daily [19,22]. It is noteworthy that this drug class reduces the risk of hospitalization for heart failure (HF) in patients at high cardiovascular risk and may contribute to a reduction in both cardiovascular and all-cause mortality [14,16,19,20,22]. Their mechanism of action, based on blocking glucose reabsorption in the proximal renal tubules, is unique because it remains insulin-independent, increases insulin sensitivity without inducing hypoglycemia, which is critical in the management of type 2 diabetes [3]. The presence of diabetes itself significantly contributes to the development of other comorbidities, such as chronic kidney disease (CKD) and heart failure, and substantially elevates cardiovascular risk [1, 2].

A particularly important element in the discussion on gliflozins is their role in restoring proper intrarenal hemodynamics. The activation of tubuloglomerular feedback, leading to the constriction of the afferent arteriole and the reduction of efferent arteriolar constriction, allows for a decrease in intraglomerular pressure. Indirectly, they act through the same mechanism as renin-angiotensin-aldosterone (RAA) system inhibitors. Furthermore, they demonstrate effects in reducing inflammation and oxidative stress, alongside limiting glomerular inflammation and fibrosis. These mechanisms explain the nephroprotective properties of these drugs, manifested by the slowing of CKD progression and a reduction in proteinuria, including in patients without diabetes [3, 4, 7,10].

In the cardiovascular context, gliflozins have shown the ability to significantly reduce hospitalizations for heart failure, as previously noted. This mechanism is likely associated not only with a reduction in cardiac preload and afterload but also with improved myocardial energetics through the utilization of ketone bodies as an alternative energy source. Additional benefits, such as weight reduction (averaging 2 kg) and the lowering of arterial blood pressure, make this drug class particularly attractive for patients with metabolic syndrome [11,13,16].

SGLT2 inhibitors demonstrate comparable clinical efficacy across age groups, establishing them as a valuable therapeutic tool in the elderly population. Their potential increases in combination therapies; the synergistic use of gliflozins with GLP-1 receptor agonists significantly reduces the risk of major cardiovascular events. Beneficial therapeutic effects are also achieved when combined with metformin or DPP-4 inhibitors [31,32,34]. The versatility and high efficacy of this drug class have been confirmed by numerous recommendations from leading scientific societies worldwide [2,5,6]. Despite a favorable safety profile, the use of gliflozins requires consideration of specific adverse effects. The most common include urogenital infections, which are a direct consequence of induced glycosuria. A critical diagnostic challenge remains euglycemic ketoacidosis (EDKA)—a rare complication that, due to the absence of significant hyperglycemia, may lead to a clinical misassessment. It should also be noted that this drug class is strictly contraindicated during pregnancy [24,30]. A significant practical limitation is the necessity to discontinue therapy 3–4 days prior to planned surgical procedures; failure to follow this protocol carries a risk of procedure postponement [3,20]. In conclusion, SGLT2 inhibitors represent a class of drugs with extensive therapeutic potential. Their mechanism of action enables not only effective regulation of glucose metabolism but also exhibits strong cardio- and nephroprotective properties. This impact translates into a reduction in all-cause mortality among patients at high risk of organ damage [4, 8].

Disclossure

Supplementary Materials

Not applicable.

Author Contributions

Conceptualization, K.T. and A.S.; resources, S.S.; data curation, W.Ś.; writing—original draft preparation, S.S. and A.S.; writing—review and editing, K.T. and W.Ś.; visualization, S.S.; supervision, K.T.; project administration, A.S. and W.Ś.

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