Molecular aspects and mechanisms of action of SGLT-2 inhibitors: beyond glycemic control.

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Abstract

Introduction: Sodium-glucose cotransporter 2 (SGLT2i) inhibitors effectively improve glycemic control and reduce body weight and cardiovascular risk. Currently, they have clear indications of heart failure and diabetic nephropathy.

Objective of the review: The present narrative study aims to describe the biochemical mechanisms involved in the beneficial effects of SGLT2i in ERD and its new indications in heart failure and chronic kidney disease.

Essential points of the review:

• SGLT2 i also has direct myocardial effects, which include the reduction of ventricular hypertrophy, the inhibition of sympathetic tone, and the natriuretic impact, which produces a decrease in systolic blood pressure of 5 mmHg.

• Metabolic effects include a decrease in serum lipids, a weight loss of 3 kilos in 6 months, and a decrease in adipose tissue at the liver level with continuous fat mass loss.

• Other experimental uses are applied in the field of cognitive impairment in diabetic patients.

Conclusion: With a diverse therapeutic effect, not limited to the single mechanism of lowering blood glucose levels, SGLT2i has new innovative indications.

Keywords:

MESH: Diabetes mellitus; Diabetes Complications; Sodium-Glucose Transporter 2 Inhibitors; Heart Failure; Renal Insufficiency, Chronic.
Diabetic kidney disease (DKD) is a frequent complication associated with diabetes mellitus (DM) and is the leading cause of end-stage kidney disease and dialysis requirements worldwide [1, 2]. ERD is directly related to cardiovascular complications, progression of chronic kidney disease (CKD), and the need for renal replacement therapy (RRT); therefore, it is essential within the treatment objectives to develop pharmacological and nonpharmacological strategies that allow for delay or cutoff of the pathogenic pathways involved in this disease. Within the pharmacological approach for treating type 2 diabetes mellitus, novel interventions have been developed with increasing evidence. These include using sodium-glucose cotransporter 2 (SGLT2) inhibitors, effectively improving glycemic control, and reducing body weight and cardiovascular risk. The present narrative review aims to describe the biochemical mechanisms involved in the beneficial effects of SGLT2 in ERD and its new indications in heart failure and chronic kidney disease.

Kidney physiology

Sodium transport

Sodium (Na+) is the most abundant cation in the extracellular fluid (ECF), with a concentration between 135 meq/l and 145 meq/l. Although it constitutes 95% of the osmolality, it is in equilibrium with the osmolarity of the intracellular fluid (ICF). Two variables regulate sodium metabolism: 1) the control of its excretion and 2) the regulation of its balance [3].

When referring to the control of urinary sodium excretion, considering a filtration rate (GFR) of 180 l/day (125 ml/min) with an average plasma sodium concentration of 140 meq/l, the filtered sodium is 25,000 meq/day. Of this amount, 24,750 (1,488 gr) are reabsorbed, and 99% of sodium is reabsorbed. Sodium filtration and reabsorption are linked in such a way as to ensure excretion despite significant fluctuations in GFR as a consequence of the tubulo-glomerular balance. On the other hand, to control reabsorption, we involve the passage of sodium from the intratubular compartment to the LIC of the tubular cell and its path from the LIC to the plasma compartment [3].

In healthy individuals, the proximal renal tubule can reabsorb all filtered glucose (approximately 180 g/day) [4]. Renal glucose reabsorption requires active basolateral elimination of sodium (Na+) by the Na+/K+-ATPase that generates the electrochemical driving force favoring the apical entry of glucose through the Na+-driven sodium-glucose cotransporter (SGLT) [4].

The first step in sodium reabsorption is due to the low concentration gradient of sodium in the LIC of the tubular cell, which creates a difference gradient between the tubular lumen and LIC, promoting spontaneous sodium influx. Subsequently, sodium must be transported in active form (countergradient) from the LIC to the plasma using the Na+-K+-ATPase pump. This active transport secretes three sodium molecules for every two potassium molecules.

The first processing of glomerular plasma ultrafiltrate occurs at the level of the renal proximal convoluted tubule (PCT), which is divided into three segments: S1 (the proximal convoluted portion), S2 (the medial convoluted portion), and S3 (the distal convoluted portion). Two-thirds of the filtered sodium will be reabsorbed in isotonic and electroneutral conditions due to the concomitant reabsorption of chloride or the simultaneous secretion of hydrogen and the reabsorption of bicarbonate [3].

Glucose transport

In the first stage of the S1, S2, and S3 segments, glucose is transported to the basolateral membrane by sodium and glucose cotransporters (SGLT1-SGLT2), accumulating glucose in the epithelium [3, 4]. The glucose gradient concentrations between the cell and the plasma lead to a second step: the passive efflux of glucose across the basolateral membrane into the plasma via the GLUT2 pathway [3]. The Na+/K+ pump maintains the sodium gradient across the apical membrane, moving sodium from the cell into the plasma.

The active transport of sodium across the apical membrane of TCP cells is mediated by a cotransporter whose main solute is glucose. The molecule must pass into the cell along the electrochemical gradient, binding to the SGLT2 symporter. SGLTs are members of the solute carrier family 5 (SLC5), which are membrane proteins that mediate the movement of glucose, osmolytes, vitamins, amino acids, and ions [5]. The SLC5 family has 12 members responsible for the cotransport of Na+ ions coupled to glucose, choline, short-chain fatty acids, and myo-inositol [6]. In the following sections, we propose to describe the effects at different levels of these cotransporters in greater detail.

Glomerular hyperfiltration in diabetic kidney disease

Glomerular hyperfiltration in diabetic kidney disease (DKD) presents early with loss of renal functional reserve. Although a universally accepted definition is lacking, we will define it as having an eGFR spontaneously elevated to two standard deviations from the average value, which varies between 130-140 ml/min per 1.73 m2 in subjects with two functioning kidneys [7, 8]. The pathogenesis of hyperfiltration is complex. Different mechanisms mediate it. Since the onset of diabetes, the kidneys will increase in size due to the expansion of the nephron due to glomerular hypertrophy (glomerulomegaly) and the proximal tubule, caused by cytokines and growth factors mediated by the hyperglycemia response (Figure 1) [9, 10].

Pre- and postglomerular factors will result in a vasoactive humoral imbalance aimed at promoting the hyperfiltration phenomenon [9, 11].
by osmotic diuresis. In this way, a significant reduction in blood pressure and afterload occurs through lipolysis and lipid oxidation, which has shown cardioprotective effects \cite{18}. These mechanisms generate a decrease in extracellular fluid, lower myocardial O2 consumption, and lower ventricular tension. Furthermore, it favors the reduction of ventricular hypertrophy with less pulmonary congestion, which has positive implications for improving peripheral edema \cite{19, 20}. Another beneficial and essential effect at the cardiovascular level is the inhibition of sympathetic tone and overactivity of the RAAS with improvement in myocardial tissue and its impact on hypertension and heart failure \cite{21}. Due to its anti-inflammatory effect, it reduces apoptosis and oxidative stress; it positively impacts cardiac remodeling, and thanks to angiogenic stimulation, there is better blood flow at the tissue level \cite{22}. Various studies, such as EMPA-REG OUTCOME, CANVAS, DECLARE, TIMI-58, VERTIS CV, DAPA-HF, DELIVER, EMPEROR-REDUCED, SOLOIST WHF, EMPEROR-PRESERVED, SCORED, CREEDENCE, and DAPA-CKD, have demonstrated a variety of positive results for major adverse cardiovascular events (MACEs). These results have been recommended in clinical practice \cite{23 – 29}.

SGLT-2i are molecules with pleiotropy, with a nonexclusive renal effect of the substrate of action, with an essential natriuretic effect that has a favorable impact on the Frank-Starling curve, with a decrease in preload, reduction of up to 5 mmHg in systolic blood pressure and up to 2 mmHg diastolic pressure, which results in an improvement in arterial stiffness and could improve endothelial function \cite{33}.

Negative fluid balance leads to lower extracellular fluid and plasma volume concentrations, reduced afterload, improved left ventricular function, and lower cardiac effort and oxygen demand \cite{34}.

At the myocardial level, iSGLT-2 can optimize cellular metabolism by generating ketone bodies, both in fasting and postprandial states, associated with improved ventricular function \cite{35}.

The study by Baartscheer et al. demonstrated that using iSGLT2 decreases the concentration of intracellular sodium and calcium in cardiomyocytes by inhibiting the Na+/Ca++ exchanger, which could exert a cardioprotective effect \cite{36}.

**Metabolic and anti-inflammatory mechanisms of SGLT-2 inhibitors**

Among the main metabolic effects of SGLT2i is to produce a state similar to fasting due to channel blockade, leading to a decrease in blood glucose, impacting HbA1c with declines of 0.5-1.0% \cite{37, 39}. The secondary reduction in insulin due to the release of glucagon increases gluconeogenesis, and by this mechanism, a decrease in lipid levels occurs through lipolysis and lipid oxidation \cite{22, 39}. Additionally, this group of drugs reduces intrarenal glucotoxicity. It thus has intrarenal anti-inflammatory effects, with a decrease in oxidative stress.

### Hemodynamic mechanisms of SGLT-2 inhibitors

iSGLT-2 has functions in various systems; it is known that at the cardiovascular level, these medications produce a decrease in blood pressure and afterload due to their natriuretic and glucosuric effects given by osmotic diuresis. In this way, a significant reduction in interstitial fluid is generated compared to the mobilization of intravascular fluid. For this reason, there is a release of water and electrolytes in the Na+/H+ [NH1] exchanger, which also allows secondary activation of the Na+/Ca++ exchanger, reducing intracellular sodium and calcium levels, which has shown cardioprotective effects \cite{18}. These mechanisms generate a decrease in extracellular fluid, lower myocardial O2 consumption, and lower ventricular tension. Furthermore, it favors the reduction of ventricular hypertrophy with less pulmonary congestion, which has positive implications for improving peripheral edema \cite{19, 20}. Another beneficial and essential effect at the cardiovascular level is the inhibition of sympathetic tone and overactivity of the RAAS with improvement in myocardial tissue and its impact on hypertension and heart failure \cite{21}. Due to its anti-inflammatory effect, it reduces apoptosis and oxidative stress; it positively impacts cardiac remodeling, and thanks to angiogenic stimulation, there is better blood flow at the tissue level \cite{22}. Various studies, such as EMPA-REG OUTCOME, CANVAS, DECLARE, TIMI-58, VERTIS CV, DAPA-HF, DELIVER, EMPEROR-REDUCED, SOLOIST WHF, EMPEROR-PRESERVED, SCORED, CREEDENCE, and DAPA-CKD, have demonstrated a variety of positive results for major adverse cardiovascular events (MACEs). These results have been recommended in clinical practice \cite{23 – 29}.

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stress, improvement in insulin sensitivity, and the function of pancreatic β-cells [40]. The result is given by reducing both fasting and post-prandial blood glucose levels [41]. A significant effect is the weight loss of 2-3 kg in 6 months, reducing adipose tissue due to the caloric loss that occurs thanks to the increase in glycosuria [21, 38, 42]. Regarding lipid metabolism, these molecules generate a decrease in triglyceride levels and an increase in HDL cholesterol, with the consequent benefit in cardiovascular risk [43, 44]. At the liver level, there is a reduction in fat content with a secondary decrease in markers of injury in hepatocytes, thus evidencing the beneficial effects on hepatic steatosis [45 – 47]. Additionally, there is a positive impact at the cardiovascular level due to the decrease in serum uric acid levels secondary to the uricosuric effect of SGLT2i [48].

By reducing glucose levels, SGLT-2i produces acute changes in glycogen and gluconeogenesis due to the early increase in glucagon levels given by paracrine inhibitory activity within the islet. It is presumed that they could act directly on alpha cells, which reduces SGLT1-dependent glucose uptake and releases glucagon, triggering hepatic glucose production mediated by glycoxygenolysis and, subsequently, gluconeogenesis. These processes prioritize using energy sources by other means, resulting in lipolysis and releasing nonesterified fatty acids to form ketones [49, 50].

Patients receiving i-SGLT2 periodically have a loss of fat mass, decreased visceral fat, and reduced steatosis, effects that are potentially beneficial for cardiovascular health [28, 36]. Promoting glycosuria provides the opportunity to have a negative energy balance, increasing caloric loss, which favors weight loss [49, 51, 52].

Additional mechanisms of SGLT-2 inhibitors

Other mechanisms that explain the reduction in oxidative stress are decreased NADPH oxidase activity, improved mitochondrial function, and glycemic control [53]. Likewise, by reducing the hyperglycemic state, there is a decrease in the expression of proinflammatory cytokines [53, 54]. It is also essential to highlight the role that ISGLT2 plays in improving endothelial dysfunction due to systemic pleiotropic effects [1, 55].

Perspectives on the use of iSGLT-2

Cardiovascular safety investigations of SGLT-2i, specifically the experience derived from studies such as Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetic Mellitus (EMPA-REG OUTCOME) with empagliflozin, CANagliflozin Cardiovascular Assessment Study (CANVAS) with canagliflozin and DECLARE-TIMI 58 with dapagliflozin, showed that they are cardioprotective, with a direct reduction in major adverse cardiovascular events (MACE) [23, 24, 26, 37]. Among the secondary results, an essential impact on renal outcomes and heart failure was evident; therefore, the benefits of this group of medications go beyond the treatment of DM (Figure 2).

Experimental use of iSGLT-2 in cancer

In cancer, it has been shown in experimental models that the expression of SGLT2 and GLUT transporters blocks glucose uptake by cancer cells. The above presumes a potential therapeutic target because metabolic reprogramming is established [36, 57].

Cognitive improvement with the use of iSGLT-2

Patients with diabetes are at increased risk of cognitive decline. SGLT2 inhibitors are fat-soluble and achieve a brain/serum ratio of 0.3 to 0.5. SGLT receptors are present in the central nervous system (CNS). Phlozins are not entirely selective for SGLT2 and have an affinity for the SGLT1 receptor, which is associated with protection against brain ischemia/reperfusion injury. SGLT2i show anti-inflammatory and anti-atherosclerotic effects, including reducing pro-inflammatory cytokines, polarization of M2 macrophages, inhibition of JAK2/STAT1 and NLRP3 inflammasome, and regression of cIMT. They also mitigate oxidative stress. SGLT2i improves endothelial function, prevents remodeling, and protects the neurovascular unit, blood-brain barrier, pericytes, astrocytes, microglia, and oligodendrocytes. Phlozins can also inhibit AChE, contributing to cognitive improvement. Empagliflozin significantly increases the level of brain BDNF, which modulates neurotransmission and ensures neuronal growth, survival, and plasticity. Furthermore, they could restore the circadian rhythm of mTOR activation, a reasonably novel finding in research on metabolic diseases and cognitive impairment. SGLT2i has...
excellent potential to protect against atherosclerosis and cognitive impairment in patients with type 2 diabetes mellitus [59].

Side effects of SGLT-2i

A recent meta-analysis, which included 13 studies with SGLT-2i and more than 90,000 patients, managed to specify some of the adverse events related to the use of SGLT-2i. In general, they are very safe medications. Consistently, these pharmacological agents increase the risk of urogenital fungal infections. However, in most cases, its treatment is usually simple. They do not increase the events of severe urinary infection, and on the other hand, the incidence of overall ketoacidosis is generally low, approximately 0.1%. An increased risk of lower limb amputations may occur in diabetic patients, primarily associated with canagliflozin; therefore, additional studies are required to identify subpopulations with an increased risk of adverse events where strict monitoring could occur. Contrary to what one might think, an essential aspect is that these medications reduce the incidence of acute kidney injury [47]. A summary of the side effects is presented in Table 1.

Table 1. Side effects of SGLT2

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Measured risk</th>
<th>Comparative risk</th>
<th>Possible associated etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary infections.</td>
<td>3 times more</td>
<td></td>
<td>Presence of urinary glucose and bad retention habits.</td>
</tr>
<tr>
<td>Lower limb amputations.</td>
<td>6.3 vs. 3.4 per thousand patients/year compared to placebo.</td>
<td>Equal risk compared to other oral antibiotics.</td>
<td>Volume depletion</td>
</tr>
<tr>
<td>Nonvertebral fractures.</td>
<td>HR 1.56 (95% CI 1.18-2.06)</td>
<td>Same risk as GLP-1</td>
<td>SGLT2-i may predispose to dehydration and increased risk of falls in older patients.</td>
</tr>
<tr>
<td>Increased serum phosphorus, PTH and FGF-23.</td>
<td>Increase of 11% phosphorus, 15% PTH and 20% FGF-23.</td>
<td></td>
<td>SGLT2 inhibition could promote phosphate reabsorption in the proximal tubule</td>
</tr>
<tr>
<td>Euglycemic diabetic ketoacidosis.</td>
<td>Unmeasured risk.</td>
<td></td>
<td>SGLT2-i increases the propensity for ketone production</td>
</tr>
<tr>
<td>Fournier's gangrene.</td>
<td>55 unique cases.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

The therapeutic effect of SGLT2i is very diverse and not limited to the single mechanism of lowering blood glucose levels. The therapeutic impact includes hemodynamic, anti-inflammatory, and pleiotropic actions. The evidence of these medications with randomized clinical studies increases daily in pathologies that were not previously targeted for use, such as heart failure and chronic kidney disease, so considering their appropriate use and side effects, SGLT-2i constitute a group of medications that meet all the requirements to be regarded as an innovative therapy.

Supplementary information

Supplementary materials have not been declared.

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Author contributions

JRF, RDA, JMH, TRY conception, article writing, and conclusions analysis. JD, VO, and CR: bibliographic search, article writing, and graph review. LCVJ: writing the abstract, review and final adjustments of the article, and analysis of the conclusions.

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Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

**Statements**

**Ethics committee approval and consent to participate**

Does not apply.

**Consent for publication**

Does not apply when images or photographs of the physical examination or X-rays/CT scans/MRI of patients are not published.

**Conflicts of interest**


Tomas Rodriguez, Lourdes Carolina Vázquez and Jaime Dulce, Carlos Restrepo and Valentina Ortiz: They do not declare a conflict of interest.

Rodrigo Daza Amedo says he has received speaking fees for Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, and Bayer. He has participated in the Advisory Board with AZ, Boehringer Ingelheim, and Novo Nordisk.

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**References**


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