REV SEN
rev-sen.ec
OPEN ACCESS

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

Tomás Rodríguez Yánez [1], Lourdes Carolina Vázquez Jiménez [2, 3], Rodrigo Andrés Daza Arnedo [4], Jaime Arturo Dulce Muñoz [5], Carlos Restrepo Guette [6], Juan Diego Montejo Hernández [4, 7], Valentina Ortiz Márquez [8], Jorge Rico Fontalvo [4, 7, 9].

1. Department of Internal Medicine, University of Cartagena, Cartagena-Colombia.
2. Department of Adult Nephrology, Faculty of Medical Sciences, National University of Asunción, Asunción-Paraguay.
3. Paraguayan Society of Nephrology, Asunción-Paraguay
4. Kidney, diabetes and metabolism Committee, Colombian Association of Nephrology and HTN, Bogotá-Colombia.
5. Department of Internal Medicine, Universidad del Sinú, Cartagena – Colombia.
6. Department of Internal Medicine, Universidad del Norte, Barraquilla – Colombia.
7. Nephrology Department, Nephromedicall IPS, Medellín-Colombia.
8. Faculty of Medicine, Universidad de la Sabana, Bogotá-Colombia
9. Faculty of Medicine, Simón Bolívar University, Barranquilla-Colombia.

Received: July 1, 2023
Accepted: July 30, 2023
Published: August 15, 2023
Editor: Dr. Franklin Mora Bravo.

Cite:
Rodríguez T, Vázquez L, Daza R, Dulce J, Restrepo C, Montejo J, Ortiz V, Rico Fontalvo J. Molecular aspects and mechanisms of action of SGLT-2 inhibitors: beyond glycemic control. REV SEN 2023;11(2):81-90.

DOI: http://doi.org/10.56867/59
SOCIEDAD ECUATORIANA DE NEFROLOGÍA DIÁLISIS Y TRASPLANTE.
ISSN-L: 2953-6448

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 Faiulre; Renal Insufficiency, Chronic.

* Corresponding author

Email: Jorge Rico Fontalvo <JorgeRicoF@yahoo.com >/Address: Street. 94 #No. 15-32 Office 309, El Chicó, Bogotá Colombia. Telephone: (+57) 315 6494495

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 (SGLT2i) 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 SGLT2i 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 osmolarity, 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, 25 meq (14 gr) are excreted, 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 chlorine 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, 5]. 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 [5]. 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 [6]. 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].

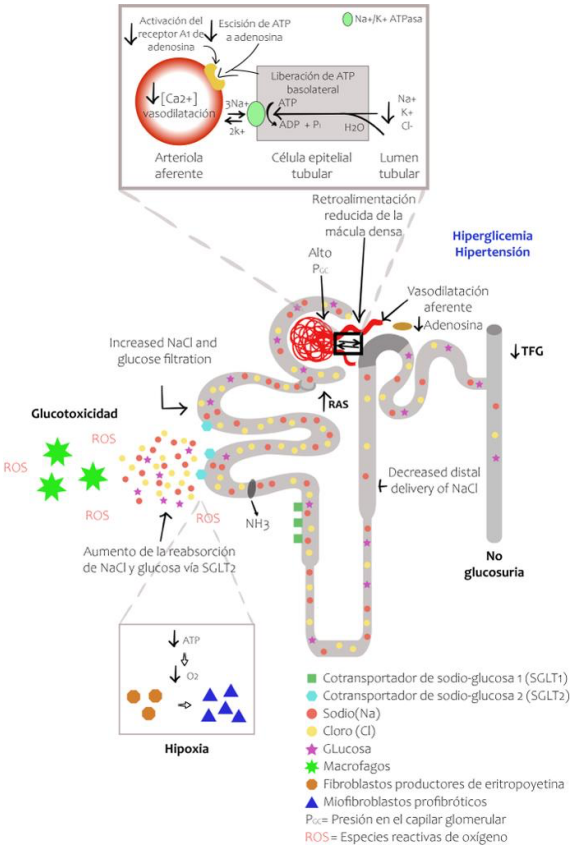

Figure 1. Renal compromise in diabetic patients. Hyperglycemia, glomerular hyperfiltration, increased glycosuria and natriuresis, glucotoxicity, renal hypoxia, increased oxidative stress, and ROS were observed. SGLT-2 inhibitors facilitate all of these renal adverse effects. Taken and adapted from Rico-Fontalvo J et al. J Clin. Nephrol 2020:4(1):44-45.

The overstimulation produced by the continuous increase in glucose stimulates the overstimulation of both SGLT receptors and sodium/hydrogen exchangers (NHE), which leads to vasodilation of the afferent arteriole and increased intrarenal filtration. [9, 12, 13]. For patients with metabolic syndrome, obesity increases intra-abdominal pressure and the accumulation of perirenal fat, which helps compress the loops of Henles. The above favors more significant tubular sodium reabsorption [8, 14, 15]. Together, glomerular hyperplasia, tubular hypertrophy, and tubular hyperabsorption decrease intratubular pressure and hydraulic pressure in Bowman's space, increasing the net pressure gradient that perpetuates hyperfiltration [8, 16, 17].

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 [18]. These mechanisms generate a decrease in extracellular fluid, lower myocardial O_2 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 [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 [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 [22]. Various studies, such as EMPA-REG OUTCOME, CANVAS, DECLARE, TIMI-58, VERTIS CV, DAPA-HF, DELIVER, EMPEROR-REDUCED, SOLOIST WHF, EMPEROR-PRESERVED, SCORED, CREDENCE, and DAPA-CKD, have demonstrated a variety of positive results for major adverse cardiovascular events (MACEs). These results have been recommended in clinical practice [23 – 32].

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 [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 [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 [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 [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% [37, 38]. 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 [22, 39]. Additionally, this group of drugs reduces intrarenal glucotoxicity. It thus has intrarenal anti-inflammatory effects, with a decrease in oxidative

stress, improvement in insulin sensitivity, and the function of pancreatic ß-cells [40]. The result is given by reducing both fasting and postprandial 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 biomarkers 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 glycogenolysis 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 SLGT2 and GLUT transporters blocks glucose uptake by cancer cells. The above presumes a potential therapeutic target because metabolic reprogramming is established [56, 57].

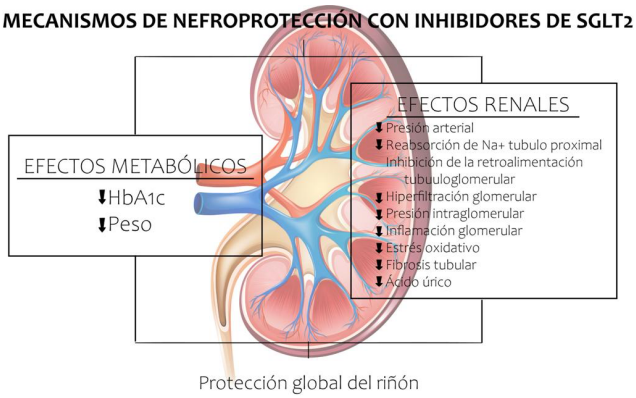

Figure 2. Mechanisms of nephroprotection with SGLT-2 inhibitors. Taken and adapted from Rico-Fontalvo J et al. J Clin. Nephrol 2020:4 (1): 44-45 [37, 58].

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

Adverse effect	Measured risk	Comparative risk	Possible associated etiology
Urinary infections.	3 times more		Presence of urinary glucose and bad retention habits.
Lower limb amputations.	6.3 vs. 3.4 per thousand patients/year compared to placebo.	Equal risk compared to other oral antibiotics.	Volume depletion
Nonvertebral fractures.	HR 1.56 (95% CI 1.18-2.06)	Same risk as GLP-1	SGLT2-i may predispose to dehydration and increased risk of falls in older patients.
Increased serum phosphorus, PTH and FGF-23.	Increase of 11% phosphorus, 15% PTH and 20% FGF-23.		SGLT2 inhibition could promote phosphate reabsorption in the proximal tubule
Euglycemic diabetic ketoacidosis.	Unmeasured risk.		SGLT2-i increases the propensity for ketone production
Acute kidney injury.	Unmeasured risk.		Unrecognized volume depletion during SGLT2i treatment. Nephrotoxicity. Uricosuria with crystal deposits, inflammation and oxidative stress.
Fournier's gangrene.	55 unique cases.		

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.

Abbreviations

iSGLT2: sodium-glucose cotransporter two inhibitors.
DRD: diabetic kidney disease.
DM: diabetes mellitus.
RRT: renal replacement therapy.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

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.

Financing

The source of the funding for this article was our resources.

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 Rodríguez, Lourdes Carolina Vázquez and Jaime Dulce, Carlos Restrepo and Valentina Ortiz: They do not declare a conflict of interest
Rodrigo Daza Arnedo 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.
Juan Montejo Hernández: He has received honoraria for lectures for Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi, Novartis, and Bayer. He has participated in the Advisory Board with AZ, Boehringer Ingelheim, and Novo Nordisk.
Jorge Rico Fontalvo declares that he has received speaking fees from Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Lilly, Sanofi, Novartis, Abbvie, Merck, and Bayer. He has participated in the Advisory Board with AZ, Boehringer Ingelheim, Bayer, and Novo Nordisk.

References

1. Rico-Fontalvo J, Daza-Arnedo R, Rodriguez-Yanez T, Martinez-Avila M, Cabrales J, Cardona-Blanco M, et al. Inflammation and Diabetic Kidney Disease: New Perspectives. J Biomed Res Environ Sci. 2022;3(7):779-86. Jelsciences/1328

2. Arnedo RD, Fontalvo JER, Salcedo NA, Alfaro M, Torrejano DN, Blanco MC, et al. Finerenone y su papel en la enfermedad renal diabética. Estado del arte. Arch Med. 2022;18(1):5. Dialnet.unirioja.es/8397843

3. Ghezzi C, Loo DDF, Wright EM. Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. Diabetologia. 2018 Oct;61(10):2087-2097. doi: 10.1007/s00125-018-4656-5. Epub 2018 Aug 22. PMID: 30132032; PMCID: PMC6133168.

4. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. Annu Rev Physiol. 2021 Feb 10;83:503-528. doi: 10.1146/annurev-physiol-031620-095920. Epub 2020 Nov 16. PMID: 33197224; PMCID: PMC8017904.

5. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011 Apr;91(2):733-94. doi: 10.1152/physrev.00055.2009. PMID: 21527736. Journals.physiology/10.1152

6. Kaur P, Behera BS, Singh S, Munshi A. "The pharmacological profile of SGLT2 inhibitors: Focus on mechanistic aspects and pharmacogenomics". Eur J Pharmacol. 2021 Aug 5;904:174169. doi: 10.1016/j.ejphar.2021.174169. Epub 2021 May 11. PMID: 33984301.

7. Cachat F, Combescure C, Cauderay M, Girardin E, Chehade H. A systematic review of glomerular hyperfiltration assessment and definition in the medical literature. Clin J Am Soc Nephrol. 2015 Mar 6;10(3):382-9. doi: 10.2215/CJN.03080314. Epub 2015 Jan 7. PMID: 25568216; PMCID: PMC4348676.

8. Tonneijck L, Muskiet MH, Smits MM, van Bommel EJ, Heerspink HJ, van Raalte DH, Joles JA. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol. 2017 Apr;28(4):1023-1039. doi: 10.1681/ASN.2016060666. Epub 2017 Jan 31. PMID: 28143897; PMCID: PMC5373460.

9. Rico Fontalvo JE. Diabetic kidney disease: from face to prevention, diagnosis and early intervention. Rev. Colomb. Nefrol. 2020;7(2). RevistaNefrologia/506

10. Hostetter TH. Hypertrophy and hyperfunction of the diabetic kidney. J Clin Invest. 2001 Jan;107(2):161-2. doi: 10.1172/JCI12066. PMID: 11160131; PMCID: PMC199186.

11. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int. 1996 Jun;49(6):1774-7. doi: 10.1038/ki.1996.265. PMID: 8743495.

12. Chagnac A, Herman M, Zingerman B, Erman A, Rozen-Zvi B, Hirsh J, Gafter U. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transplant. 2008 Dec;23(12):3946-52. doi: 10.1093/ndt/gfn379. Epub 2008 Jul 12. PMID: 18622024.

13. Muskiet MH, Smits MM, Morsink LM, Diamant M. The gut-renal axis: do incretin-based agents confer renoprotection in diabetes? Nat Rev Nephrol. 2014 Feb;10(2):88-103. doi: 10.1038/nrneph.2013.272. Epub 2013 Dec 24. Erratum in: Nat Rev Nephrol. 2014 Jul;10(7):362. PMID: 24375052.

14. Alonso-Galicia M, Dwyer TM, Herrera GA, Hall JE. Increased hyaluronic acid in the inner renal medulla of obese dogs. Hypertension. 1995 Apr;25(4 Pt 2):888-92. doi: 10.1161/01.hyp.25.4.888. PMID: 7721449.

15. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001 Jun;12(6):1211-1217. doi: 10.1681/ASN.V1261211. PMID: 11373344.

16. Persson P, Hansell P, Palm F. Tubular reabsorption and diabetes-induced glomerular hyperfiltration. Acta Physiol (Oxf). 2010 Sep;200(1):3-10. doi: 10.1111/j.1748-1716.2010.02147.x. Epub 2010 May 27. PMID: 20518753; PMCID: PMC2919631.

17. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J Am Soc Nephrol. 1999 Dec;10(12):2569-76.

doi: 10.1681/ASN.V10122569. PMID: 10589696.

18. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61(10):2108-2117. doi: 10.1007/s00125-018-4670-7. Epub 2018 Aug 22. PMID: 30132036.

19. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, Rossing P, Groop PH, Cooper ME. Diabetic kidney disease. Nat Rev Dis Primers. 2015 Jul 30;1:15018. doi: 10.1038/nrdp.2015.18. PMID: 27188921; PMCID: PMC7724636.

20. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. Diabetes Obes Metab. 2018 Mar;20(3):479-487. doi: 10.1111/dom.13126. Epub 2017 Nov 15. PMID: 29024278.

21. Scheen AJ. Effect of SGLT2 Inhibitors on the Sympathetic Nervous System and Blood Pressure. Curr Cardiol Rep. 2019 Jun 21;21(8):70. doi: 10.1007/s11886-019-1165-1. PMID: 31227915.

22. Lopera Vargas JM, Rico Fontalvo JE, Melgarejo R. E, Castillo Barrios GA, Ramírez Rincón A, Gomez AM, Martínez Rojas S, Ibatá Bernal L. Effect of pharmacological therapies for glycemic control in patients with type 2 diabetes mellitus on vascular outcomes. Rev. Colomb. Nefrol. 2020;7(1). doi: 10.22265/acnef.7.1.372

23. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.

24. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al.; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12. PMID: 28605608.

25. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al.; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019 Jun 13;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.

26. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019 Jan 24;380(4):347-357. doi: 10.1056/NEJMoa1812389. Epub 2018 Nov 10. PMID: 30415602.

27. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.

28. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377.

29. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021 Jan 14;384(2):117-128. doi: 10.1056/NEJMoa2030183. Epub 2020 Nov 16. PMID: 33200892.

30. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al.; SCORED Investigators. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021 Jan 14;384(2):129-139. doi: 10.1056/NEJMoa2030186. Epub 2020 Nov 16. PMID: 33200891.

31. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.

32. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. ;DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446. doi: 10.1056/NEJMoa2024816. Epub 2020 Sep 24. PMID: 32970396.

33. Verma S, McMurray JJV, Cherney DZI. The Metabolodiuretic Promise of Sodium-Dependent Glucose Cotransporter 2 Inhibition: The Search for the Sweet Spot in Heart Failure. JAMA Cardiol. 2017 Sep 1;2(9):939-940. doi: 10.1001/jamacardio.2017.1891. PMID: 28636701.

34. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose cotransporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs. 2015 Jan;75(1):33-59. doi: 10.1007/s40265-014-0337-y. PMID: 25488697.

35. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, et al. Empagliflozin Increases Cardiac Energy Production in Diabetes: Novel Translational Insights Into the Heart Failure Benefits of SGLT2 Inhibitors. JACC Basic Transl Sci. 2018 Aug 26;3(5):575-587. doi: 10.1016/j.jacbts.2018.07.006. PMID: 30456329; PMCID: PMC6234616.

36. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na+ through inhibition of the cardiac Na+/H+ exchanger in rats and rabbits. Diabetologia. 2017 Mar;60(3):568-573. doi: 10.1007/s00125-016-4134-x. Epub 2016 Oct 17. PMID: 27752710; PMCID: PMC6518059.

37. Rico-Fontalvo J, Daza-Arnedo R, Cardona-Blanco MX, Leal-Martínez V, Abuabara-Franco E, Pajaro-Galvis N, et al. SGLT2 Inhibitors and nephroprotection in diabetic kidney disease: From mechanisms of action to the latest evidence in the literature. J Clin Nephrol. 2020;4(1):044-55. Heighpubs.org/jcn/1058

38. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Feb 4;75(4):422-434. doi: 10.1016/j.jacc.2019.11.031. Erratum in: J Am Coll Cardiol. 2020 Sep 22;76(12):1505. PMID: 32000955.

39. Storgaard H, Gluud LL, Bennett C, Grøndahl MF, Christensen MB, Knop FK, Vilsbøll T. Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. PLoS One. 2016 Nov 11;11(11):e0166125. doi: 10.1371/journal.pone.0166125. PMID: 27835680; PMCID: PMC5106000.

40. Mordi IR, Lang CC. Glucose-Lowering and Metabolic Effects of SGLT2 Inhibitors. Heart Fail Clin. 2022 Oct;18(4):529-538. doi: 10.1016/j.hfc.2022.03.004. PMID: 36216483.

41. DeFronzo RA, Reeves WB, Awad AS. Pathophysiology of diabetic kidney disease: impact of SGLT2 inhibitors. Nat Rev Nephrol. 2021 May;17(5):319-334. doi: 10.1038/s41581-021-00393-8. Epub 2021 Feb 5. PMID: 33547417.

42. Bonora BM, Avogaro A, Fadini GP. Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence. Diabetes Metab Syndr Obes. 2020 Jan 21;13:161-174. doi: 10.2147/DMSO.S233538. PMID: 32021362; PMCID: PMC6982447.

43. Garnica-Cuéllar JC, Lavalle-González FJ, Magaña-Serrano JA, Almeda-Valdés P, Cetina-Canto JA, Chávez-Iñíguez JS, et al. Documento de consenso sobre el uso de los iSGLT2 en el tratamiento de pacientes con diabetes mellitus tipo 2 [Consensus on the use of iSGLT2 in the treatment of patients with type 2 diabetes mellitus]. Gac Med Mex. 2022 Jan 28;158(Monografic 1):1-14. Spanish. doi: 10.24875/GMM.M21000596. PMID: 35080818.

44. Pollock C, Neuen BL. Sodium-Glucose Cotransporter 2 Inhibition: Rationale and Mechanisms for Kidney and Cardiovascular Protection in People With and Without Diabetes. Adv Chronic Kidney Dis. 2021 Jul;28(4):298-308. doi: 10.1053/j.ackd.2021.02.006. PMID: 34922686.

45. Sattar N, Fitchett D, Hantel S, George JT, Zinman B. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomized trials including the EMPA-REG OUTCOME® trial. Diabetologia. 2018 Oct;61(10):2155-2163. doi: 10.1007/s00125-018-4702-3. Epub 2018 Jul 31. PMID: 30066148; PMCID: PMC6133166.

46. Leiter LA, Forst T, Polidori D, Balis DA, Xie J, Sha S. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. Diabetes Metab. 2016 Feb;42(1):25-32. doi: 10.1016/j.diabet.2015.10.003. Epub 2015 Nov 11. PMID: 26575250.

47. Yaribeygi H, Maleki M, Reiner Ž, Jamialahmadi T, Sahebkar A. Mechanistic View on the Effects of SGLT2 Inhibitors on Lipid Metabolism in Diabetic Milieu. J Clin Med. 2022 Nov 4;11(21):6544. doi: 10.3390/jcm11216544. PMID: 36362772; PMCID: PMC9653639.

48. Zhao Y, Xu L, Tian D, Xia P, Zheng H, Wang L, Chen L. Effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2018 Feb;20(2):458-462. doi: 10.1111/dom.13101. Epub 2017 Sep 27. PMID: 28846182.

49. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia. 2018 Oct;61(10):2098-2107. doi: 10.1007/s00125-018-4669-0. Epub 2018 Aug 22. PMID: 30132034.

50. Ferrannini E. Sodium-Glucose Cotransporters and Their Inhibition: Clinical Physiology. Cell Metab. 2017 Jul 5;26(1):27-38. doi: 10.1016/j.cmet.2017.04.011. Epub 2017 May 11. PMID: 28506519.

51. Cai X, Yang W, Gao X, Chen Y, Zhou L, Zhang S, Han X, Ji L. The Association Between the Dosage of SGLT2 Inhibitor and Weight Reduction in Type 2 Diabetes Patients: A Meta-Analysis. Obesity (Silver Spring). 2018 Jan;26(1):70-80. doi: 10.1002/oby.22066. Epub 2017 Nov 22. PMID: 29165885.

52. Kurinami N, Sugiyama S, Nishimura H, Morita A, Yoshida A, Hieshima K, Miyamoto F, Kajiwara K, Jinnouchi K, Jinnouchi T, Jinnouchi H. Clinical Factors Associated with Initial Decrease in Body-Fat Percentage Induced by Add-on Sodium-Glucose Cotransporter 2 Inhibitors in Patient with Type 2 Diabetes Mellitus. Clin Drug Investig. 2018 Jan;38(1):19-27. doi: 10.1007/s40261-017-0580-6. PMID: 29098566; PMCID: PMC5762773.

53. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, Takasu T, Imamura M, Li Q, Tomiyama H, Kobayashi Y, Noda A, Sasamata M, Shibasaki M. Effects of sodium-glucose cotransporter 2 selective inhibitor ipragliflozin on hyperglycemia, oxidative stress, inflammation and liver injury in streptozotocin-induced type 1 diabetic rats. J Pharm Pharmacol. 2014 Jul;66(7):975-87. doi: 10.1111/jphp.12223. Epub 2014 Feb 17. PMID: 24533859.

54. Garvey WT, Van Gaal L, Leiter LA, Vijapurkar U, List J, Cuddihy R, Ren J, Davies MJ. Effects of canagliflozin versus glimepiride on adipokines and inflammatory biomarkers in type 2 diabetes. Metabolism. 2018 Aug;85:32-37. doi: 10.1016/j.metabol.2018.02.002. Epub 2018 Feb 13. PMID: 29452178.

55. Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, Bruno RM. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol. 2017 Oct 23;16(1):138. doi: 10.1186/s12933-017-0621-8. PMID: 29061124; PMCID: PMC5654086.

56. Hung MH, Chen YL, Chen LJ, Chu PY, Hsieh FS, Tsai MH, Shih CT, Chao TI, Huang CY, Chen KF. Canagliflozin inhibits growth of hepatocellular carcinoma by blocking glucose-influx-induced β-catenin activation. Cell Death Dis. 2019 May 29;10(6):420. doi: 10.1038/s41419-019-1646-6. PMID: 31142735; PMCID: PMC6541593.

57. Dutka M, Bobiński R, Francuz T, Garczorz W, Zimmer K, Ilczak T, Ćwiertnia M, Hajduga MB. SGLT-2 Inhibitors in Cancer Treatment-Mechanisms of Action and Emerging New Perspectives. Cancers (Basel). 2022 Nov 25;14(23):5811. doi: 10.3390/cancers14235811. PMID:

36497303; PMCID: PMC9738342.

58. Rico-Fontalvo J, Vázquez-Jiménez LC, Rodríguez-Yánez T, Daza-Arnedo R, Vergara-Serpa O, Uparella I, et al. Inhibidores de SGLT-2 en Nefropatía Lúpica. Podria considerarse una intervención de Nefroprotección. Rev Paraguaya Reumatol. diciembre de 2022;8(2):94-100. Revista.spr.py/169

59. Pawlos A, Broncel M, Woźniak E, Gorzelak-Pabiś P. Neuroprotective Effect of SGLT2 Inhibitors. Molecules 2021;26(23):7213. doi: 10.3390/molecules26237213. PMID: 34885795; PMCID: PMC8659196.

DOI: Digital Object Identifier. PMID: PubMed Identifier.

Editor's Note

REV SEN remains neutral concerning jurisdictional claims over published maps and institutional affiliations.