SGLT2 INHIBITOR - A NEW HYPOGLYCEMIC AGENTS WITH POTENTIAL EFFECT IN CARDIOVASCULAR RISK

"An apple a day keeps heart failure, kidney disease, and myocardial infarction away"

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Abstract

Type 2 diabetes mellitus, along with complications that accompany it, have become a major threatening life disease in the 21st century. Although the association between glycated hemoglobin (HbA1c) and macrovascular complications has been known for many years, antidiabetic drugs have not been able to reduce these problems. The 2019 European Association of Cardiology/European Association for the Study of Diabetes guidelines on diabetes, prediabetes and heart disease recommend sodium-glucose cotransporter 2 inhibitors (SGLT2i) over metformin as first-line therapy in patients with atherosclerotic cardiovascular disease (ASCVD) or high or very high risk. Unlike many other antihyperglycemic therapies, increasing glucose excretions via SGLT2 inhibition provides hypoglycemic effects independent of insulin. The use of SGLT2 inhibitors may have beneficial effects on biomarkers such as blood glucose, blood pressure, body weight, intrarenal hemodynamics and proteinuria, and may also reduce cardiovascular complications, kidney disease and diabetes. The American Diabetes Association now recommends the use of SGLT2 inhibitors after initial treatment with dietary and lifestyle changes in addition to metformin in patients with T2DM and all cardiovascular diseases, including heart failure. SGLT2 inhibitors will become an important tool in the hands of physicians in daily practice targeting this vulnerable population.

Key words: SGLT2**,** cardiovascular, heart failure, inhibition, glycemic

FRENUESIT SGLT2 - NJË AGJENT I RI HIPOGLICEMIK ME EFEKT POTENCIAL NË RREZIKUN KARDIOVASKULAR

Abstrakt

Diabeti Melitus tip 2, së bashku me komplikacionet e tij, është një sëmundje jetëkërcënuese në shekullin e 21-të. Edhe pse lidhja midis hemoglobinës së glukozuar (HbA1c) dhe komplikacioneve makrovaskulare është e njohur për shumë vite, preparatet antidiabetike nuk kanë qenë në gjendje t'i reduktojnë këto komplikacione. Udhëzimet e Shoqatës Evropiane të Kardiologjisë 2019/Shoqatës Evropiane për Studimin e Diabetit, për diabetin, prediabetin dhe

sëmundjet e zemrës, rekomandojnë frenuesit e bashkëtransportuesit natrium -glukozë 2 (SGLT2) mbi metforminën, si terapi të linjës së parë në pacientët me sëmundje aterosklerotike kardiovaskulare (ASCVD), me rrezik të lartë ose shumë të lartë. Ndryshe nga shumë terapi të tjera antihiperglicemike, rritja e ekskretimit të glukozës nëpërmjet frenimit të SGLT2 siguron efekte hipoglicemike të pavarura nga insulina. Përdorimi i SGLT2i mund të ketë efekte të dobishme në biomarkerët si glukoza në gjak, presioni i gjakut, pesha trupore, hemodinamika intrarenale dhe proteinuria, si dhe mund të reduktojë komplikacionet kardiovaskulare, sëmundjet e veshkave dhe diabetin. Shoqata Amerikane e Diabetit tani rekomandon përdorimin e frenuesve SGLT2 pas trajtimit nëpërmjet ndryshimit të stilit të jetesës dhe rregjimit dietetik, përveç metforminës, në pacientët me DM tip 2 dhe të gjitha sëmundjet kardiovaskulare, përfshirë insuficiencën kardiake. Frenuesit SGLT2 do të jenë një mjet i rëndësishëm në duart e mjekëve, në praktikën e përditshme, duke patur synim këtë grup popullatë.

Fjalë kyç: SGLT2, kardiovaskular, insuficiencë kardiake, frenim, glicemik

Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic disease. Its prevalence has increased over the past several decades. T2DM is associated with an increased risk of several cardiovascular diseases (CVD), with heart failure (HF) being a more common early symptom than myocardial infarction (MI) (1). Patients with heart failure often have insulin resistance, which may eventually promote the development of diabetes or worsen it. Several large cohort studies have reported a prevalence of diabetes in patients with heart failure of 30–50%, further suggesting a link between the two diseases (1). In 2008, the US Food and Drug Administration issued pharmaceutical industries to assess the cardiovascular outcome of antidiabetic therapy, beyond glycemic control (2). Prior to the advent of gliflozin, no antidiabetic therapy had shown significant improvement in HF hospitalizations (3). Therefore, SGLT2 inhibitors, also known as gliflozin, represent an effective and innovative treatment option for patients with T2DM.

The origin of SGLT2i can be traced to phlorizin, an organic compound first discovered and extracted from the bark of the apple tree, by De Koninck and Stas in 1835 (4). SGLT1 is expressed mainly in the proximal renal tubules of the nephrons, small intestine, and myocardium, while SGLT2i is found only in the brush borders of epithelial cells in the S1 and S2 segments of the proximal renal tubules. Its expression and activity are increased by increased plasma glucose but do not inhibit renal gluconeogenesis, which may be increased in diabetes, and cause osmotic diuresis in individuals with or without diabetes (5). Administration of SGLT2i results in a daily loss of 60–100 g of glucose in the urine, thereby reducing energy expenditure and leading to significant changes in the body's metabolism (6). SGLT2i treatment has been associated with significant improvements in insulin resistance and insulin secretion. In addition, SGLT2 inhibitors directly stimulate the α cells of the pancreas to increase glucagon secretion. This reduces hepatic triglyceride synthesis, reduces liver fat and blood triglyceride concentration, and increases liver ketone body production (7). Therefore, SGLT2 inhibitor therapy improves many atherosclerotic risks in patients with type 2 diabetes. SGLT2 inhibitors also have hemodynamic effects: they increase urine output and sodium loss, thereby reducing body weight and systolic and diastolic blood pressure (8,9).

This medication goes beyond glycemic control and has been shown to be effective in the medium- to long-term treatment of T2DM complications. SGLT2 inhibitors have also shown significant reductions in cardiovascular events, heart failure hospitalizations, and cardiovascular and all-cause mortality (10–13). Over the past 5 years, evidence from randomized controlled trials (RCTs) has demonstrated unequivocal efficacy and safety for most cardiovascular (CV) and renal outcomes, independent of the effect on glycemic control. In patients with high risk of ASCVD or established ASCVD, GLP-1RA or SGLT2 inhibitors should be considered; in patients with CKD or heart disease failure with reduced ejection fraction, SGLT2 inhibitors should be the first choice. Given the beneficial cardiovascular and metabolic effects of SGLT2 inhibitors, they may be useful in preventing cardiovascular disease in patients with T2DM and a history of cardiovascular disease. SGLT2 inhibitors are also useful in the primary and secondary prevention of in-hospital heart failure in patients with T2DM and various risk factors.

Although SGLT2i were initially considered and developed as hypoglycemic agents, they unexpectedly noted a reduction in mortality and cardiovascular events and demonstrated cardiorenal protection even in the absence of hyperglycemic status. The results were seen regardless of the presence of diabetes, if the patients were male or female, young or old, or receiving neprilysin inhibitors. This combination of results is unique among current heart failure drugs (14).

Cardiac benefits

The four direct effects of SGLT2i on the myocardium are: improvement of the energy and metabolism of the myocardium; reduction of mass and hypertrophy of the left ventricle as well as apoptosis of cardiomyocytes; reduction of myocardial inflammation and the level of proinflammatory cytokines; improvement of myocardial and ECM remodeling (15).

The dual natriuretic and diuretic effects of SGLT2 affect the reduction of intra- and extracellular volume, and the reduction of intravascular volume and arterial pressure decreases the load before and after cardiac surgery, thus influencing the relief of cardiac load and improving left ventricular function (16). The cardio-renal effects of SGLT2 natriuresis inhibitors are mediated by inhibition of the myocardial sodium-proton exchanger, and have been shown to reduce cardiac hypertrophy and heart failure (17). Through glycosuria induced by SGTLT2, it affects a wide range of metabolic changes that can reduce both fibrosis and the creation of plaques, all of which are related to the heart. Based on previous studies, SGLT2 can reduce both myocardial fibrosis and cardiac remodeling by regulating macrophage morphology, as well as protect the heart from ischemia/reperfusion injury (18-20). One of the effects of SGLT2, which helps to reduce the unfavorable remodeling of heart failure, is realized between the reduction of the epicardial fat mass and the level of inflammatory cytokines such as tumor necrosis factor-a and plasminogen activator inhibitor-1 in diabetic patients with CVD (21). It has been speculated that SGLT2 increases the concentration of mitochondrial calcium through the direct inhibitory effect of the sodium-hydrogen (Na+/H+) exchange in the myocardium, influencing in this way the improvement of mitochondrial function and the reduction of oxidation (17). All of the above-mentioned mechanisms underlie the cardioprotective effects of SGLT2, including the reduction of cardiac interstitial fibrosis, coronary fibrosis, arterial thickness, cardiac interstitial macrophage infiltration, and cardiac superoxide levels. In various research studies, it has

been reported that empagliflozin increases the utilization of fatty acids, ketone bodies, and branched-chain amino acids, decreases ATP inhibition, increases myocardial ATP, and increases fuel consumption in diabetic cardiomyopathy rats, which affect in increasing their cardiac activity (22).

Renal benefits

The American Diabetes Association/European Association for the Study of Diabetes now recommends the use of SGLT2 inhibitors after initial therapy with dietary and lifestyle modifications in addition to metformin in patients with T2DM and all cardiovascular diseases, including heart failure (23,24). SGLT2 inhibitors will become an important tool in the hands of physicians in daily practice targeting this group population.

SGLT2 inhibitors not only reduce proteinuria, but also preserve eGFR and reduce the risk of end-stage renal disease (25,26). SGLT2i have been shown to reduce HbA1c levels without causing hypoglycemic events. In the long term, lowering blood sugar and improving insulin resistance may reduce microvascular complications. SGLT2i inhibits the toxic effects of high glucose on the proximal renal tubular cells by causing oxidative stress and advanced glycation endproducts, p21-mediated senescence, and the production of proinflammatory and profibrotic mediators (27). This protection by SGLT2i is related to the development of renal failure. On the other hand, there is a protective effect of associated with altered renal hemodynamics. SGLT2 inhibition increases distal sodium transport, which promotes glomerular feedback and results in an improvement in intraglomerular pressure (28) – slowing the progression of kidney disease. At the same time, the effect of urinary sodium is associated with a decrease in blood pressure, usually around 4 mmHg systolic and 2 mmHg diastolic (29), exerting an indirect kidney-protective effect. They also have to deal with weight loss due to the loss of sugar (calories) in the urine and the osmotic diuresis caused by sugar (30), and we know that obesity is one of the most important factors for incipient CKD (31).

In addition, SGLT-2i reduce blood uric acid in patients with type 2 diabetes, which is useful given the evidence that hyperuricemia is a risk factor for hypertension, kidney disease, and heart disease. The mechanism is that high glucose levels in the renal tubules facilitate the exchange of glucose and urate, leading to increased urinary excretion of urate (32). Thus, there are multiple direct and indirect mechanisms that may influence the reno-protective effects of SGLT2i (33).

In **conclusion**, we believe that this drug class is becoming important in the treatment of heart and kidney disease, given the bidirectional nature of cardio-renal interactions and the predisposition of T2DM patients to heart failure and kidney disease. Considering the origin of SGLT2i we can say “An apple a day keeps heart failure, kidney disease, and myocardial infarction away”.

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References

1. Shah, A.D.; Langenberg, C.; Rapsomaniki, E.; et.al. Type 2 diabetes and incidence of cardiovascular diseases: A cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015, 3, 105–113. [CrossRef]
2. Hwang, T.; Franklin, J.; Kesselheim, A. Effect of US Food and Drug Administration's Cardiovascular Safety Guidance on Diabetes Drug Development. Clin. Pharmacol. Ther. 2017, 102, 290–296. [CrossRef]
3. Custodio, J.S.; Duraes, A.R.; Abreu, M.; Rocha, N.A.; Roever, L. SGLT2 inhibition and heart failure—current concepts. Heart Fail. Rev. 2018, 23, 409–418. [CrossRef]
4. Ehrenkranz, J.R.L.; Lewis, N.G.; Kahn, C.R.; Roth, J. Phlorizin: A Review. Diabetes Metab. Res. Rev. 2005, 21, 31–38. [CrossRef] [PubMed]
5. Daniel Hssia, Owen Grove, William T Cefalu. An update on SGLT2 inhibitors for the treatment of Diabetes Mellitus. 1st Ed, 2018
6. Kashiwagi A, Araki S, Maegawa H. Sodium-glucose cotransporter 2 inhibitors represent a paradigm shift in the prevention of heart failure in type 2 diabetes patients. J Diabetes Investig. 2021 Jan;12(1):6-20. doi: 10.1111/jdi.13329. Epub 2020 Aug 5. PMID: 32563214; PMCID: PMC7779279
7. Cefalu WT. Paradoxical insights into whole body metabolic adaptations following SGLT2 inhibition. J Clin Invest 2015;124: 485–487
8. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015; 38: 420–428.
9. Kashiwagi A, Yoshida S, Kawamura K, et al. Effects of ipragliflozin, a selective sodium–glucose co-transporter 2 inhibitor, on blood pressure in Japanese patients with type 2 diabetes mellitus: a pooled analysis of six randomized, placebo-controlled clinical trials. Diabetol Int 2017; 8: 76–86
10. Zelniker, T.A.; Braunwald, E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors. J. Am. Coll. Cardiol. 2020, 75, 422–434. [CrossRef]
11. Swoboda, P.P.; McDiarmid, A.K.; Erhayiem, B.; et al. Diabetes Mellitus, Microalbuminuria, and Subclinical Cardiac Disease: Identification and Monitoring of Individuals at Risk of Heart Failure. J. Am. Heart Assoc. 2017, 6. [CrossRef]
12. Lenti, M.V.; Pasina, L.; Cococcia, S.; Cortesi, L.; et al. Mortality rate and risk factors for gastrointestinal bleeding in elderly patients. Eur. J. Intern. Med. 2019, 61, 54–61. [CrossRef]
13. Palmiero G, Cesaro A, Vetrano E, et.al. Impact of SGLT2 Inhibitors on Heart Failure: From Pathophysiology to Clinical Effects. Int J Mol Sci. 2021 May 30;22(11):5863. doi: 10.3390/ijms22115863. PMID: 34070765; PMCID: PMC8199383.
14. Zannad, Faiez, et al. "SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials." The Lancet 396.10254 (2020): 819-829.
15. Sabouret P, Galati G, Angoulvant D, Germanova O, Castelletti S, et al (2020) The interplay between cardiology and diabetology: a renewed collaboration to optimize cardiovascular prevention and heart failure management. Eur Heart J Cardiovasc Pharmacother 13:pvaa051. https://doi.org/10.1093/ehjcvp/pvaa051
16. Kario K, Okada K, Kato M, et al. 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA Study. Circulation. 2018;139(18):2089–2097.

17. Packer, M.; Anker, S.D.; Butler, J.; Filippatos, G.; Zannad, F. Effects of sodiumglucose cotransporter 2 inhibitors for the treatment of patients with heart failure: Proposal of a novel mechanism of action. JAMA Cardiol. 2017, 2, 1025–1029. [CrossRef]
18. Vallon, V.; Thomson, S.C. Targeting renal glucose reabsorption to treat hyperglycaemia: The pleiotropic effects of SGLT2 inhibition. Diabetologia 2017, 60, 215–225. [CrossRef] [PubMed]
19. Lee, T.M.; Chang, N.C.; Lin, S.Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. Free Radic. Biol. Med. 2017, 104, 298–310. [CrossRef] [PubMed]
20. Lim, V.G.; Bell, R.M.; Arjun, S.; Kolatsi-Joannou, M.; Long, D.A.; Yellon, D.M. SGLT2 inhibitor, canagliflozin, attenuates myocardial infarction in the diabetic and nondiabetic heart. J. Am. Coll. Cardiol. Basic. Trans. Science. 2019, 4, 15–26. [CrossRef]
21. Sato, T.; Aizawa, Y.; Yuasa, S.; Kishi, S.; et al. The effect of dapagliflozin treatment on epicardial adipose tissue volume. Cardiovasc. Diabetol. 2018, 17, 1–9. [CrossRef] [PubMed]
22. Verma, S.; Rawat, S.; Ho, K.L.; Wagg, C.S.; Zhang, L.; Teoh, H.; Lopaschuk, G.D. Empagliflozin increases cardiac energy production in diabetes: Novel translational insights into the heart failure benefits of SGLT2 inhibitors. J. Am. Coll. Cardiol. Basic Trans. Sci. 2018, 3, 575–587.
23. J.B. Buse, D.J. Wexler, A. Tsapas, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Diabetologia, 63 (2020), pp. 221-228
24. American Diabetes Association. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2021 Diabetes Care, 44 (2021), pp. S111-S124.
25. O. Mosenzon, S.D. Wiviott, A. Cahn, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial Lancet Diabetes Endocrinol, 7 (2019), pp. 606-617.
26. Nelaj, E., Kecaj, I., Feracaku, J., Xhixhabesi, K., & Tase, M. (2024). Benefits of SGLT2 inhibitors on renal and cardiovascular protection, in diabetic patients. South Eastern European Journal of Public Health, 200–206. https://doi.org/10.70135/seejph.vi.689
27. Podestà, M.A.; Sabiu, G.; Galassi, A.; Ciceri, P.; Cozzolino, M. GLT2 Inhibitors in Diabetic and Non-Diabetic Chronic Kidney Disease. Biomedicines 2023, 11, 279. https://doi.org/10.3390/ biomedicines11020279
28. Anders, H.-J.; Davis, J.M.; Thurau, K. Nephron Protection in Diabetic Kidney Disease. N. Engl. J. Med. 2016, 375, 2096–2098. [CrossRef] [PubMed]
29. Chao EC. SGLT-2 Inhibitors: A New Mechanism for Glycemic Control. Clin Diabetes. 2014 Jan;32(1):4-11. doi: 10.2337/diaclin.32.1.4. PMID: 26246672; PMCID: PMC4521423.
30. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, Mari A, Pieber TR, Muscelli E (2016) Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes. 65(5):1190–1195

31. Kovesdy CP, Furth SL, Zoccali C (2017) Obesity and kidney disease: hidden consequences of the epidemic. Afr J Prim Health Care Fam Med 26:9(1)
32. Musso G, Gambino R, Cassader M, Pagano G: A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 44:375–393, 2012
33. Storgaard, H.; Gluud, L.L.; Bennett, et.al. 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, 11, e0166125.