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Extraglycemic effects of SGLT2 inhibitors on endothelial function and inflammation: A literature review

Efeitos extraglicêmicos dos inibidores de SGLT2 na função endotelial e inflamação: Uma revisão de literatura

Efectos extraglucémicos de los inhibidores de SGLT2 sobre la función endotelial y la inflamación: Una revisión de la literatura

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Abstract
Sodium–glucose cotransporter 2 (SGLT2) inhibitors have demonstrated cardiovascular benefits that extend beyond glycemic control, particularly in the context of coronary artery disease (CAD). This article synthesizes mechanistic and clinical evidence on SGLT2 inhibitors in coronary artery disease (CAD), with emphasis on inflammation, endothelial function, mitochondrial homeostasis, oxidative stress, and cardiac remodeling. A narrative literature review was conducted using the PubMed/MEDLINE, Embase, and Scopus databases (2015–2025), including experimental studies (in vitro/in vivo), clinical trials, and cohort studies published in Portuguese, English, or Spanish. Case reports and studies with insufficient clinical information were excluded. No protocol was registered; PRISMA and formal risk-of-bias assessment were not applied. Findings were organized thematically (molecular mechanisms; inflammation/endothelium; mitochondria; oxidative stress; clinical relevance to CAD). SGLT2 inhibitors lower pro-inflammatory mediators (e.g., TNF-α, IL-6, IL-1β), inhibit NLRP3 inflammasome activation, and favor M2 macrophage polarization. They preserve endothelial integrity—via AMPKα1/ULK1/FUNDC1-dependent mitophagy, reduced ROS, and increased NO bioavailability—and modulate cardiomyocyte metabolism, impacting infarct size and remodeling in experimental models. Clinically, the evidence supports extraglycemic benefits, particularly in patients with type 2 diabetes mellitus (T2DM) and cardiovascular risk. Convergent anti-inflammatory, antioxidant, and endothelial/mitochondrial effects support an adjunctive role of SGLT2 inhibitors in high-risk CAD profiles, while underscoring the need for randomized trials targeting CAD/MI-specific outcomes.
Keywords: Sodium-Glucose Transporter 2 Inhibitors; Coronary Artery Disease; Vascular Endothelium; Mitochondrial Dysfunction; Myocardial Infarction.

Resumo

Os inibidores do cotransportador sódio–glicose 2 (SGLT2) têm demonstrado benefícios cardiovasculares que extrapolam o controle glicêmico, particularmente no contexto da doença arterial coronariana (DAC). Este artigo sintetiza evidências mecanísticas e clínicas sobre os inibidores do cotransportador sódio–glicose 2 (SGLT2) na doença arterial coronariana (DAC), com ênfase em inflamação, função endotelial, homeostase mitocondrial, estresse oxidativo e remodelamento cardíaco. Foi realizada uma revisão narrativa da literatura nas bases PubMed/MEDLINE, Embase e Scopus (2015–2025), incluindo estudos experimentais (in vitro/in vivo), ensaios clínicos e coortes em português, inglês ou espanhol. Relatos de caso e estudos com informação clínica insuficiente foram excluídos. Não houve protocolo registrado, nem aplicação de PRISMA ou avaliação formal de risco de viés. A síntese foi temática (mecanismos moleculares; inflamação/função endotelial; mitocôndria; estresse oxidativo; relevância clínica para DAC). Os inibidores de SGLT2 reduzem mediadores pró-inflamatórios (p.ex., TNF-α, IL-6, IL-1β), inibem a ativação do inflamassoma NLRP3 e favorecem a polarização M2 de macrófagos. Preservam a integridade endotelial—incluindo mitofagia dependente de AMPKα1/ULK1/FUNDC1, menor geração de ROS e maior biodisponibilidade de NO—e modulam vias metabólicas do cardiomiócito, com impacto sobre tamanho de infarto e remodelamento em modelos experimentais. Em âmbito clínico, os achados apoiam benefícios extraglicêmicos sobretudo em pacientes com diabetes mellitus tipo 2 (DM2) e risco cardiovascular. Os efeitos convergentes anti-inflamatórios, antioxidantes e endoteliais/mitocondriais sustentam um papel adjuvante dos inibidores de SGLT2 em perfis de alto risco com DAC, reforçando a necessidade de ensaios randomizados focados em desfechos específicos de DAC/IAM.

Palavras-chave: Inibidores do Transportador 2 de Sódio-Glicose; Doença Arterial Coronariana; Endotélio Vascular; Doenças Mitocondriais; Infarto do Miocárdio.

Resumen

Los inhibidores del cotransportador sodio–glucosa tipo 2 (SGLT2) han demostrado beneficios cardiovasculares que van más allá del control glucémico, particularmente en el contexto de la enfermedad arterial coronaria (EAC). Este artículo sintetiza evidencias mecanísticas y clínicas sobre los inhibidores del cotransportador sodio–glucosa tipo 2 (SGLT2) en la enfermedad arterial coronaria (EAC), con énfasis en la inflamación, la función endotelial, la homeostasis mitocondrial, el estrés oxidativo y el remodelado cardíaco. Se realizó una revisión narrativa de la literatura en las bases de datos PubMed/MEDLINE, Embase y Scopus (2015–2025), incluyendo estudios experimentales (in vitro/in vivo), ensayos clínicos y estudios de cohortes publicados en portugués, inglés o español. Se excluyeron reportes de caso y estudios con información clínica insuficiente. No hubo protocolo registrado; no se aplicó PRISMA ni una evaluación formal del riesgo de sesgo. La síntesis fue temática (mecanismos moleculares; inflamación/endotelio; mitocondria; estrés oxidativo; relevancia clínica para EAC). Los inhibidores de SGLT2 reducen mediadores proinflamatorios (p. ej., TNF-α, IL-6, IL-1β), inhiben la activación del inflamasoma NLRP3 y favorecen la polarización M2 de macrófagos. Preservan la integridad endotelial—mediante mitofagia dependiente de AMPKα1/ULK1/FUNDC1, menor ROS y mayor biodisponibilidad de NO—y modulan el metabolismo del cardiomiocito, con impacto en el tamaño del infarto y la remodelación en modelos experimentales. En el ámbito clínico, la evidencia respalda beneficios extraglucémicos, especialmente en pacientes con diabetes mellitus tipo 2 (DM2) y riesgo cardiovascular. Efectos convergentes antiinflamatorios, antioxidantes y endoteliales/mitocondriales respaldan un papel adyuvante de los inhibidores de SGLT2 en perfiles de alto riesgo con EAC, y subrayan la necesidad de ensayos aleatorizados centrados en desenlaces específicos de EAC/IM.

Palabras clave: Inhibidores del Cotransportador de Sodio-Glucosa 2; Enfermedad de la Arteria Coronaria; Disfunción Endotelial; Enfermedades Mitocondriales; Infarto del Miocardio.

1. Introduction

It was a significant milestone in clinical pharmacology when the sodium–glucose cotransporter type 2 (SGLT2) was identified, enabling targeted pharmacological intervention in glucose management. The natural product phlorizin, discovered in 1835, led to the development of selective, potent, and safe SGLT2 inhibitors. Among the members currently in clinical practice, dapagliflozin (DAPA), empagliflozin (EMPA), and canagliflozin (CANA) have demonstrated efficacy in various metabolic and cardiovascular conditions (Rosenwasser et al., 2013). These drugs were initially developed for the treatment of type 2 diabetes mellitus (T2DM) and act by inhibiting renal proximal tubular glucose reabsorption, resulting in glucosuria and a reduction in blood glucose levels. Beyond blood glucose, new evidence demonstrates extraglycemic benefits, including effects on systemic inflammation, oxidative stress, endothelial function, heart failure, and reduction in coronary artery disease (CAD) and diabetic nephropathy (Vallon, 2024; Vallon & Verma, 2021). CAD is a heterogeneous condition with an atherosclerotic basis, characterized by abnormal perfusion in the coronary system. It is the basis for the presence of angina,

acute heart attack (acute myocardial infarction - AMI), and sudden death. Still, it represents one of the leading causes of death in Brazil and in the world (Malakar et al., 2019). In this context, we have conducted a narrative literature search of SGLT2 inhibitor studies in CAD, focusing on potential mechanisms of cardiovascular protection and current evidence for their emerging role in patients at high cardiovascular risk (Mone et al., 2022). This article aims to synthesize mechanistic and clinical evidence on sodium–glucose cotransporter 2 (SGLT2) inhibitors in coronary artery disease (CAD), focusing on inflammation, endothelial function, mitochondrial homeostasis, oxidative stress, and cardiac remodeling.

2. Methodology

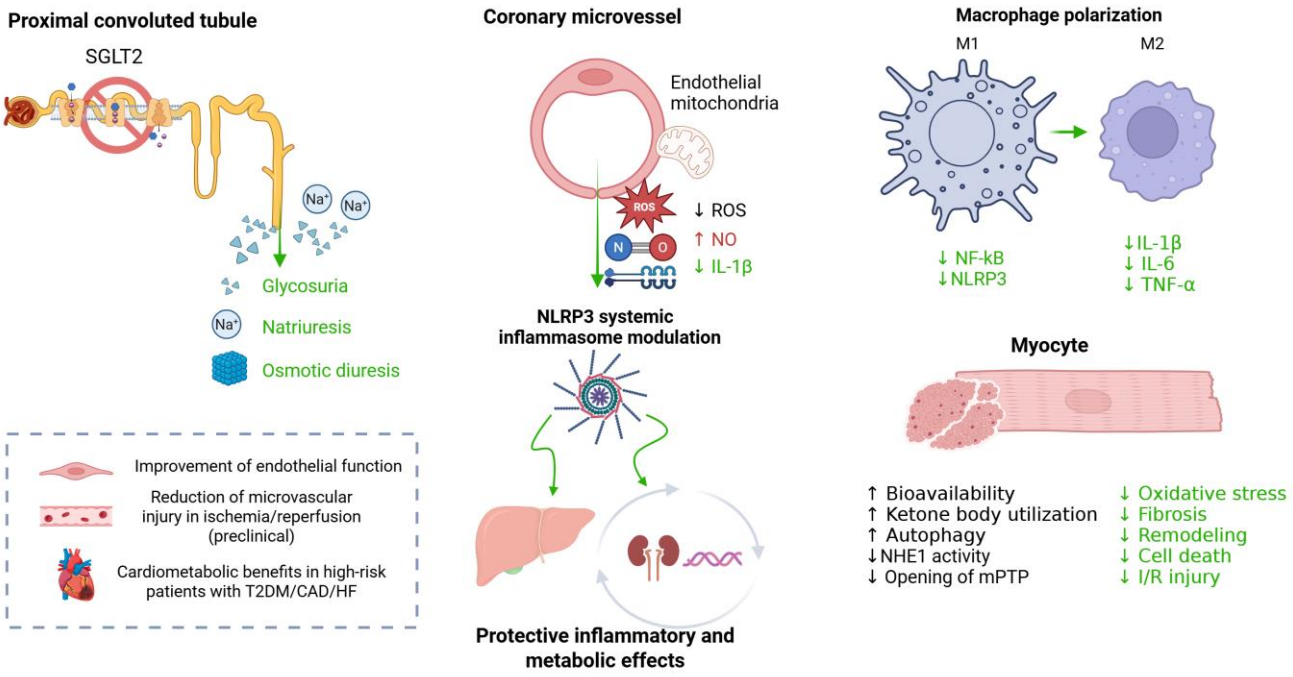
We carried out a qualitative investigation (Pereira et al., 2018), having a narrative search (Rother, 2007) in the PubMed/MEDLINE, Embase, and Scopus databases, without prior protocol registration, covering publications from 2015 to 2025, in English, Portuguese, or Spanish. We used combinations of descriptors related to "Sodium-Glucose Transporter 2 Inhibitors"; "Coronary Artery Disease"; "Vascular Endothelium"; "Mitochondrial Dysfunction" and "Myocardial Infarction". We include experimental studies (in vitro/in vivo), clinical trials, cohorts, and reviews relevant to the scope. The selection was made by a reviewer, with eligibility checked by the senior author. As this is a narrative review, we did not apply the PRISMA checklist or conduct a formal risk-of-bias assessment. We performed a targeted literature search, excluding case reports and studies with insufficient clinical information, and synthesized the eligible evidence qualitatively. Extracted data were organized thematically across mechanistic and clinical domains, molecular mechanisms, inflammation and endothelial function, mitochondrial function, oxidative stress, and clinical relevance to coronary artery disease. No protocol was registered.

3. Results and Discussion

3.1 Renal mechanisms and systemic effects of SGLT2 inhibitors

DAPA, EMPA, and CANA inhibit the SGLT2 in the S1 segment of the proximal convoluted tubule, reducing renal glucose reabsorption and promoting glucosuria (with mild natriuresis/osmotic diuresis). This insulin-independent mechanism lowers plasma glucose levels and is typically accompanied by modest weight loss and reductions in blood pressure, contributing to a favorable cardiometabolic profile in T2DM (Bocchi et al., 2021). Because glucose-lowering occurs without stimulating insulin secretion, these agents do not induce hyperinsulinemia and may reduce exogenous insulin requirements when used in combination therapy (Tang et al., 2017). Beyond these renal effects, SGLT2 inhibitors exert systemic and cardiovascular actions that extend to inflammation, endothelial function, mitochondrial homeostasis, and cardiomyocyte metabolism, as summarized in Figure 1.

Figure 1 - Potential extraglycemic mechanisms of SGLT2 inhibitors in coronary artery disease (CAD).



Source: Authors.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors act primarily in the proximal renal tubule, promoting glucosuria, natriuresis, and mild osmotic diuresis, which are thought to contribute to cardiometabolic benefits beyond glucose lowering. In the coronary microvasculature, these agents indirectly improve endothelial function by reducing reactive oxygen species (ROS), increasing nitric oxide (NO) bioavailability, and modulating systemic NLRP3 inflammasome activation, particularly under ischemia/reperfusion (I/R) conditions. SGLT2 inhibition has been associated with modulation of immune responses by suppressing pro-inflammatory M1 macrophage polarization and promoting an anti-inflammatory M2 phenotype, accompanied by reduced NF-κB signaling and lower secretion of interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α). In cardiomyocytes, SGLT2 inhibitors enhance mitochondrial homeostasis, increase ketone body utilization, stimulate autophagy, inhibit pathological Na^+/H^+ exchanger 1 (NHE1) activity, and limit mitochondrial permeability transition pore (mPTP) opening. Collectively, these mechanisms contribute to reduced oxidative stress, fibrosis, adverse cardiac remodeling, cell death, and myocardial injury, supporting a potential cardioprotective, extraglycemic role of SGLT2 inhibitors in patients with CAD, particularly those with type 2 diabetes mellitus and high cardiovascular risk. Abbreviations: ROS, reactive oxygen species; NO, nitric oxide; NLRP3, NOD-like receptor pyrin domain-containing 3; NF-κB, nuclear factor kappa B; IL-1β, interleukin-1 beta; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; NHE1, Na^+/H^+ exchanger 1; mPTP, mitochondrial permeability transition pore; I/R, ischemia/reperfusion; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; HF, heart failure. Created in BioRender.

3.2 Effect of SGLT2 inhibitors on inflammation and endothelium

The anti-inflammatory action of SGLT2 inhibitors is not restricted to the modulation of blood glucose levels. Some studies have demonstrated reduced levels of TNF-α, IL-6, and IL-1β, as well as blockade of the NLRP3 inflammasome (Kim et al., 2020; Rykova et al., 2025). In viral and hypoglycemic inflammation, DAPA promotes M2 macrophage polarization via a STAT3-dependent pathway, facilitating tissue repair (Yan et al., 2022). DAPA and EMPA have also been reported to reduce the activities of IL-1β and NLRP3, which are essential for atherogenesis, and to attenuate NF-κB and IL-6 expression, thereby

leading to protection against vascular damage and suppression of atherogenesis. Notably, in ApoE$^{-/-}$ mice fed a Western diet, empagliflozin significantly reduced the area of atherosclerotic lesions, along with decreased expression of inflammatory markers such as IL-1β and IL-6, and downregulation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous activity. In vitro, EMPA was also shown to inhibit IL-1β expression in oxLDL-stimulated macrophages by suppressing NF-κB signaling (Liu et al., 2021; Scisciola et al., 2022). Furthermore, EMPA reduces NLRP3 activation and the production of pro-inflammatory cytokines (IL-18, IL-1β), as well as macrophage infiltration in cardiac tissue (Byrne et al., 2020). EMPA reduces microvascular injury and loss of endothelial integrity in I/R models by AMPKα1/ULK1/FUNDC1-dependent mitophagy, leading to the inhibition of oxidative stress and apoptosis in microvascular endothelial cells (Cai et al., 2022).

3.3 Mitochondrial dysfunction

Mitochondrial abnormalities play a key role in the development of various cardiometabolic diseases, such as HTN (Lahera et al., 2017), obesity (Cojocaru et al., 2023), and CAD (Jia et al., 2021). In CAD, the production of ROS is increased, leading to reduced NO availability and impaired endothelial function (Wilson et al., 2023). SGLT2 inhibitors alleviate mitochondrial oxidative stress, as evidenced by decreases in hs-CRP, myeloperoxidase, ICAM-1, and IL-6, as well as NF-κB-p65, along with increases in superoxide dismutase-1 and glutathione (Mone et al., 2022). This protective effect is exerted on renal cells against hyperglycemia-induced damage. EMPA reverses mitochondrial and cellular damage under hypoxia, at least in part through AMPKα1/ULK1 and FUNDC1-dependent mitophagy, leading to decreased ROS and enhanced NO release, and correlated with inhibitory effects on TNF-α and iNOS in human cardiac endothelial cells (Chen et al., 2023).

3.4 Oxidative stress

Oxidative stress refers to an imbalance between ROS production and the cellular ability to detoxify or repair damage caused by these species. DAPA invariably responds to improving oxidative stress in cardiac injury. Treatment reduces superoxide/nitrotyrosine, restores STAT3 signaling, and restrains mPTP formation—thereby preserving microcirculation and endothelial integrity during I/R (Hsieh et al., 2022). In human EC exposed to hyperglycemia, DAPA attenuates iNOS-mediated oxidative stress in part via Nrf2/HO-1 and mitophagy signaling (Zhou et al., 2023). Another key mechanism of action of empagliflozin (EMPA) is its ability to modulate the Na^+/H^+ exchanger (NHE) in endothelial cells. Under inflammatory and stress conditions, NHE becomes overactivated, leading to increased cytoplasmic sodium levels ($[Na^+]_a$), which in turn stimulates the Na^+/Ca^{2+} exchanger (NCX) and promotes reactive oxygen species (ROS) generation via pathways such as NADPH oxidase activation and mitochondrial dysfunction (Li et al., 2024). Empagliflozin reduces NHE activity and intracellular sodium accumulation, thereby attenuating NCX overstimulation, lowering oxidative stress, and increasing nitric oxide (NO) bioavailability. These actions contribute to the preservation of endothelial integrity, microvascular perfusion, and overall cardiac function (Zuurbier et al., 2021).

3.5 Actions on cardiomyocytes and cardiac remodeling

Treatment of pressure overload in the myocardium involves controlling remodeling, which is regulated by cardiomyocyte hypertrophy and the development of fibrosis. At AMI, cardiomyocyte energy metabolism is reprogrammed, with main features including a reduction in fatty acid oxidation and an increase in glucose and ketone body catabolism. This modification is believed to be achieved also due to the inhibition of pyruvate dehydrogenase and a discrepancy between glycolysis and ATP synthesis (Doenst et al., 2013; Jiang et al., 2021). EMPA promotes an improved metabolic state by

increasing the utilization of ketone bodies, activating the antioxidant protective system, and counteracting low-grade activation of fatty acid oxidation, thereby reducing apoptosis and early mortality in experimental models (Oshima et al., 2019). Ordinarily, cells use autophagy to protect themselves when under stress. However, when autophagy fails, it can lead to a type of cell death known as autosis. Autosis is a non-apoptotic autophagy-based suicide. It is associated with increased adherence of cell substrates, focal distension of perinuclear space, and ER distension and fragmentation. EMPA modulates this balance between the axis—the promotion of beneficial autophagy and inhibition of autosis—and the AMPK/Beclin-1-mediated pathway is involved in the (de)regulation of infarct size, fibrosis, and survival in AMI experimental models (Huang et al., 2025; Makrecka-Kuka et al., 2020; Wang et al., 2022).

3.6 Comparison to Brazilian, American, and European CAD guidelines

All major guidelines consistently recommend SGLT2 inhibitors for the management of cardiometabolic conditions, particularly to reduce risk. The 2021 Brazilian Society of Cardiology guidelines recommend SGLT2 inhibitors in all patients, independent of HbA1c, supported by studies such as DECLARE (sub-analysis in previous AMI). The 2023 American Heart Association guidelines recommend the use of SGLT2 inhibitors in T2DM patients with established cardiovascular disease, as there is evidence that these medications decrease cardiovascular risk in such patients (Class I, Level A)(Virani et al., 2023). The 2024 European Society of Cardiology guidelines recommend the use of SGLT2 inhibitors in chronic coronary syndrome and T2DM with Class I, level A evidence (Vrints et al., 2024). If we combine those recommendations, there is a consistent net benefit, although the dosages, exact indications, and so on differ.

Limitations: This work is a literature review (narrative) and, therefore, does not follow a systematic protocol with double screening, meta-analysis, or formal assessment of risk of bias. Thus, there is a possibility of selection and publication bias. Even so, transparency was sought in the search strategy, inclusion criteria, and the distinction between mechanistic and clinical evidence.

4. Conclusion

The evidence gathered suggests that SGLT2 inhibitors exert extraglycemic effects — including anti-inflammatory, antioxidant, and endothelial/mitochondrial preservation — with potential relevance for patients with coronary artery disease, especially when T2DM and/or heart failure coexist. Additional studies, preferably randomized trials focused on specific clinical outcomes of CAD/AMI, are needed to consolidate indications and target populations.

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