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Protective Potential of Sodium-Glucose Cotransporter 2 Inhibitors in Internal Medicine (Part 2)

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Abstract
Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are now uncovering new possibilities in the field of internal medicine owing to their diverse protective effects. In the second part of the literature review, we explore potential applications of SGLT2i in hepatology, neurology, ophthalmology, and oncology, mechanisms of action of such drugs as dapagliflozin, empagliflozin, canagliflozin, etc, and their effect on different organs and systems.

Keywords: hepatoprotection, neuroprotection, retinoprotection, oncoprotection, dapagliflozin, empagliflozin, canagliflozin
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Протективный потенциал ингибиторов натрий-глюкозного котранспортера 2 типа в клинике внутренних болезней (часть 2)

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Резюме
Ингибиторы натрий-глюкозного котранспортера 2-го типа (SGLT2i) открывают новые горизонты в клинике внутренних болезней благодаря многообразию своих протективных эффектов. Во второй части данного обзора мы анализируем потенциал SGLT2i в области гепатологии, неврологии, офтальмологии и онкологии, рассматривая механизмы действия таких препаратов, как дапаглифлозин, эмпаглифлозин, канаглифлозин и др., а также их влияние на различные органы и системы.
Ключевые слова: SGLT2i, гепатопротекция, нейропротекция, ретинопротекция, онкопротекция, дапаглифлозин, эмпаглифлозин, канаглифлозин
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Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially developed as blood glucose lowering agents.[1] However, from the very beginning of their clinical use, a wide range of pleiotropic properties was established.[2-4]

The relevance of studying the protective potential of SGLT2i is increasing due to the accumulation of data indicating their hepatoprotective, neuroprotective, and even oncoprotective properties. Although these findings are promising, it should be emphasized that these effects are not fully understood yet and require further detailed analysis, in particular in the absence of carbohydrate metabolism disorders.

Therefore, this review article aims to detail the protective potential of SGLT2i and their significance in areas, such as hepatology, neurology, ophthalmology, and oncology. Addressing these topics is vital to clarify controversies surrounding the SGLT2i use in treating not only type 2 diabetes (T2D) but also various comorbidities. A comprehensive understanding of such nuances will assist clinicians with more informed decision-making and improve quality of patient care.

Discussion

SGLT2i in Hepatology

SGLT2i represent a promising group of drugs with potential metabolic effects that may be useful in hepatology, especially in nonalcoholic fatty liver disease (NAFLD).[5] The mechanism underlying the NAFLD pathogenesis involves insulin resistance and hyperglycemia, highlighting the importance of studying the role of SGLT2i in this area.[6]

The sodium-glucose cotransporter 2 (SGLT2) expression was detected not only in the kidney but also in the liver, as demonstrated by immunostaining and immunoblotting (SGLT2 intensity: kidney 165.8±15.6, liver 114.4±49.0 arbitrary units). The stratified analysis showed no significant differences in hepatic SGLT2 expression based on age, sex, body mass index, or severity of the liver disease. However, in the undirected graphical model, SGLT2 was found to interact directly with various factors, including sex and fatty change, neutrophil-to-lymphocyte ratio, triglyceride, hemoglobin A1c, creatinine, and albumin (partial correlation coefficient 0.4-0.6 for sex and 0.2-0.4 for others).[7] Analyzing approaches of the Japan Society of Hepatology, as outlined in the 2020 clinical practice guidelines, SGLT2i may be one of the most effective treatments for NAFLD in the presence of T2D.

Studies indicate that SGLT2i aid in reducing fat mass, including liver fat content. Canagliflozin was found to improve hepatic insulin sensitivity and slow triglyceride accumulation in the liver, ultimately leading to more significant weight loss than in the control group.[8] Furthermore, SGLT2i play a vital role in regulating lipid metabolism by decreasing low-density lipoprotein levels.[9]

Long-term use of SGLT2i has resulted in notable improvements in liver fibrosis markers in patients with NAFLD. After 24 weeks of SGLT2i therapy (canagliflozin,[10] empagliflozin[11]), there was a significant improvement in fibrotic changes in liver biopsy specimens.

After 6 months of treatment, there was a significant reduction in liver steatosis indices, accompanied by lower levels of circulating pro-inflammatory markers, such as interleukin-1β, interleukin-6, tumor necrosis factor, vascular endothelial growth factor, and monocyte chemoattractant protein-1.[12]

In a retrospective multicenter study, investigating effects of SGLT2i in 1262 patients with NAFLD complicated by T2D,[13] 202 participants were ultimately included in the final analysis. This study demonstrated that SGLT2i administration over a period of 48 weeks not only improved glycemic control but also led to reductions in body weight, uric acid levels, transaminases, etc. Recent findings suggest that SGLT2i may also alleviate NAFLD severity in patients with T2D.

In a study involving empagliflozin, participants experienced noticeable declines in serum levels of plasminogen activator inhibitor-1, γ-glutamyltransferase, leptin, and visceral fat area after 12 weeks, suggesting a beneficial impact on the liver function.[14] Furthermore, after 24 weeks of treatment, there were reductions in body mass index, waist circumference, and fasting blood glucose levels, along with improvements in markers of liver dysfunction.[15]

In a meta-analysis,[16] a total of 6 trials involving 309 patients with NAFLD and T2D indicated that SGLT2i can significantly reduce alanine aminotransferase (ALT) levels ($P=.01$) as well as the magnetic resonance imaging proton density fat fraction ($P=.02$). In addition, secondary outcomes, such as body weight and visceral fat area, also decreased.

A meta-analysis of 19 randomized controlled trials[17] revealed that therapy with SGLT2i notably reduced levels of ALT, aspartate aminotransferase (AST), and γ-glutamyltransferase. Furthermore, SGLT2i led to a significant increase in bilirubin levels. However, no significant changes in albumin levels were observed following SGLT2i treatment.

Another meta-analysis of 8 articles[18] encompassing 686 patients indicated that SGLT2i significantly reduced liver stiffness measurement compared with controls. Further subgroup analyses revealed that SGLT2i presented more advantages with longer treatment duration and more serious steatosis in decreasing liver stiffness measurement. As for controlled attenuation parameter, SGLT2i had a clear advantage in subgroup analyses of longer treatment duration, younger age, dapagliflozin treatment, worse fibrosis, and steatosis.

It is noteworthy that the hepatoprotective effects of SGLT2i are not contingent on the presence of metabolic syndrome or T2D. For instance, a study conducted on an experimental model of methotrexate-induced hepatotoxicity revealed that intraperitoneal administration of empagliflozin (30 mg/kg/day) to Wistar rats resulted in an improvement in markers of liver cytolytic syndrome and restoration of redox homeostasis.[19] These findings were further corroborated by a pathomorphological examination of the liver, which highlighted the morpho-stabilizing potential of empagliflozin.

Additionally, dapagliflozin efficacy has been demonstrated in models of cisplatin-induced hepatotoxicity. Oral administration of dapagliflozin at a dose of 0.9 mg/kg/day was associated with the stabilization of serum parameters, including total protein, albumin, bilirubin, AST, ALT, and the AST/ALT ratio. Furthermore, a reduction in hepatocyte degeneration and necrosis was noted.[20]

By analyzing the above-mentioned data, we can conclude that SGLT2i show considerable promise in the management of both NAFLD and toxic (drug-induced) hepatitis. However, despite their potential, current options are still insufficient for widespread clinical application, underscoring the necessity for further research on the clinical efficacy and mechanisms of action of SGLT2i, particularly in the context of comprehensive treatment strategies for liver diseases.

SGLT2i in Ophthalmology

Diabetic retinopathy (DR) is one of the most serious complications of T2D and the leading cause of blindness in adults.[21] By the time visual impairment occurs, the optimal window for therapy has usually expired.[22] Studies demonstrated SGLT2 expression in bovine and murine retinal pericytes, with significant increases in SGLT2 messenger RNA levels in the retina of mice with T2D.[23] Despite isolated reports,[24] no reliable data have been found on the detection of SGLT2 expression in the human retina. However, there is a high probability that SGLT2 is involved in the pathogenesis of DR, which opens new opportunities for its prevention and treatment using SGLT2i.[25]

Hyperglycemia triggers 4 molecular pathways associated with oxidative stress, protein glycosylation, and, ultimately, retinal damage: the aberrant polyol pathway, the inositol pathway, the accumulation of advanced glycation end products, and the activation of protein kinase C.[26] It is well known that microvascular complications in T2D are associated with hyperglycemia; a 1% decrease in glycated hemoglobin A_{1c} (HbA_{1c}) levels can reduce the risk of microvascular complications by 37%.[27] In the first week of treatment, SGLT2i can reduce fasting blood glucose by approximately 1.5 mmol/L and effectively reduce HbA_{1c} by approximately 1.5%, equivalent to a daily dose of 2000 mg metformin.[28]

Clinical studies have shown various benefits of dapagliflozin treatment on vascular remodeling after 6 weeks; the dapagliflozin group demonstrated a decrease in retinal arteriolar permeability compared with the placebo group, which had an increase in the vessel wall-to-lumen ratio, indicating retinal vascular wall remodeling.[29] In addition, SGLT2i were found to reduce pericyte edema and excess extracellular matrix production.[30]

Recent studies have suggested a correlation between SGLT2 expression and sympathetic nervous system activity. Hyperactivation of the sympathetic nervous system is characteristic of obesity and T2D.[31] Norepinephrine, the main neurotransmitter of the sympathetic nervous system, has been shown to increase SGLT2 protein expression in human renal proximal tubule cells.[32] Moreover, mice fed a high-fat diet and treated with dapagliflozin showed decreased tyrosine hydroxylase expression and norepinephrine levels in both cardiac and renal tissues.[33] Sympathetic overactivation in an experimental model of hypertension was associated with axonal damage in the outer retinal layers; these data suggest that SGLT2i may be useful in preventing retinal damage related to sympathetic overactivation.

In terms of retinoprotective potential, it is worth noting the mild antihypertensive and lipid-lowering effects of SGLT2i.[34] Studies confirmed that, on average, every 10 mm Hg decrease in systolic blood pressure leads to a 13% reduction of the risk of diabetic microvascular complications, and strict blood pressure control can reduce the risk of blindness in DR by 47%.[35]

Dyslipidemia also contributes to the DR development. DR exudates are deposits of lipids and proteins that occur in the outer plexiform layer of the retina. The number of exudates was positively correlated with triglyceride, low-density lipoprotein, and total cholesterol levels and negatively correlated with high-density lipoprotein levels.[36] A decrease in low-density lipoprotein and very low-density lipoprotein levels was observed in patients treated with SGLT2i.[37]

According to a nationwide retrospective cohort study involving 3 432 911 adults with T2D in Taiwan, the combined use of metformin and SGLT2i could reduce the risk of DR progression. Short-term use of SGLT2i could significantly increase the risk of DR, whereas long-term use of SGLT2i could significantly reduce it.[38]

In summary, SGLT2i are widely used for the clinical treatment of T2D. However, the data on their efficacy in the DR treatment are mainly obtained from animal experiments, indicating a great potential for clinical trials of SGLT2i in the DR treatment.

SGLT2i in Oncology

Approximately a century ago, the concept of the Warburg effect was introduced, highlighting that tumor cells act as metabolic traps, resulting in significantly higher glucose consumption compared with normal cells.[39] This phenomenon laid the foundation for considering cancer as a metabolic disease; altered glucose metabolism leads to several characteristic features, including accelerated cell growth, angiogenesis, metastasis, and evasion of apoptosis.[40]

In this regard, SGLT2i appear promising because SGLT2 is actively expressed not only in the proximal tubules of the kidneys but also in tumor cells, which exhibit increased expression and translocation of glucose transporters (specifically GLUT1 and GLUT3), as well as various glycolytic enzymes due to the reprogramming of their glucose metabolism.[41]

The anticancer properties of SGLT2i may occur across a variety of cancer types.[42] Potential mechanisms of action include reduced glucose uptake by tumor cells, decreased glucose availability to cancer cells, interruption of the cell cycle and DNA replication, and alterations in various signaling pathways and the expression of genes and proteins.[43] The overall antiproliferative effects of SGLT2i can be attributed to their lowered glucose levels and uptake in various in vitro and in vivo models.

Thus, inhibition of glucose transport may be combined with impairment of the mitochondrial membrane potential, suppression of β-catenin and phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (mTOR) pathways, and promotion of the initiation of apoptosis and other mechanisms.[44-48] Specifically, canagliflozin inhibits the proliferation and survival of breast cancer cells (MCF7) by targeting mitochondrial complex I, which disrupts cellular respiration and enhances activity of AMP-activated protein kinase (AMPK).[49] SGLT2i promoted cell cycle arrest in the G1/G0 phase and induced apoptosis in MCF7 cells; they inhibited oxidative phosphorylation and ATP synthesis but increased AMPK phosphorylation while blocking the mTOR.[50]

Specifically, this effect was attributed to the disruption of β-catenin translocation from the cytoplasm to the nucleus, where its degradation is directly mediated by inhibition of protein phosphatase 2A (PP2A) activity.[50] Furthermore, canagliflozin decreased cell proliferation and enhanced the clonogenic survival of PC3 prostate cancer cells, both alone and in conjunction with ionizing radiation and docetaxel.[47]

Importantly, SGLT2i possess several noncanonical effects that enhance their anticancer properties independent of glucose regulation. These include reducing angiotensin levels and promoting osmotic diuresis by increasing plasma renin activity, which leads to a decrease in blood pressure and an increase in urinary sodium excretion.[51] Additionally, SGLT2i block myocardial Na+/H+ exchange, resulting in elevated mitochondrial sodium concentrations in patients with heart failure.[52]

These agents are also associated with improved myocardial metabolism, potentially contributing to enhanced oxygen supply and uptake and facilitating a metabolic shift from glucose to ketone bodies. These properties may significantly bolster the anticancer effects of SGLT2i.

The sympatholytic properties of SGLT2i may help diminish the sympathetic hyperactivity associated with various forms of cancer. These sympatholytic effects could play a significant role in the anticancer properties of SGLT2i, particularly considering recent findings that inhibiting β2-adrenergic signaling (reducing sympathetic activity) within the tumor microenvironment can enhance the effectiveness of chemotherapeutic agents such as doxorubicin in triple-negative breast cancer models.[53]

The integration of SGLT2i, especially in conjunction with traditional chemotherapy, is a promising strategy in oncology, particularly for patients with both cancer and T2D. Nonetheless, further clinical trials are needed to validate their additive effects and overall benefits. The multifaceted effects of these drugs may contribute to slowing tumor progression and improving cardiovascular and T2D-related outcomes. However, safety and clinical feasibility remain critical limitations that underscore the need for more comprehensive research.

Given the potential of SGLT2i in oncology, along with their promising applications in cardiology, it is imperative to direct special attention to SGLT2i studies within the realm of cardio-oncology.[54] Cardiotoxicity associated with chemotherapeutic agents, particularly doxorubicin, remains a significant concern in clinical practice.[55-57]

In a study conducted by our research team utilizing an author's model of chronic toxic-ischemic cardiomyopathy,[58] we evaluated the effects of dapagliflozin on parameters associated with cardiovascular disease resulting from the administration of doxorubicin and cyclophosphamide. These findings indicate that dapagliflozin contributes to the improvement of oxidative status, lipid metabolism, endothelial function, and inflammatory response, ultimately facilitating structural and functional normalization of the cardiovascular system, and underline the need for further investigation of the SGLT2i role in cardio-oncology.

SGLT2i in Neurology

Glycemic control of SGLT2i has previously been considered a key mechanism for their cognitive effects.[59,60] Several studies have linked the neuroprotective effects of SGLT2i with the correction of endothelial dysfunction.[61] There are also studies showing the importance of correcting mitochondrial disorders in the development of the neuroprotective effects of SGLT2i.[62]

Of particular interest is that SGLT2i are lipid-soluble and therefore able to penetrate the blood-brain barrier. Thus, SGLT2i may act on the SGLT1/SGLT2 cotransporter, which is widely expressed in the brain, thereby reducing neuroinflammation, apoptosis, and oxidative stress.[63] In addition, SGLT2i have been shown to inhibit both acetylcholinesterase and SGLT2, thereby increasing brain-derived neurotrophic factor levels.[64,65]

In a study using Mendelian randomization, SGLT1i demonstrated a significant association with a reduced risk of amyotrophic lateral sclerosis and multiple sclerosis. In contrast, SGLT2i are associated with an increased risk of Alzheimer disease and dementia with Lewy bodies. In addition, elevated HbA_{1c} levels, independent of the effects of SGLT1 and SGLT2 blockade, are associated with an increased risk of Parkinson disease.[66]

SGLT2i use may be associated with neuroprotective effects in T2D patients, reducing the incidence or progression of dementia.[67] Based on an analysis of 6 observational studies involving 460 112 patients with T2D without dementia, of whom 155 844 received SGLT2i and 304 268 received non-SGLT2i controls with a median follow-up of 2.8 years (range, 1.3-11.4 years). The incidence of dementia was 2.7% in the SGLT2i group and 8.7% in the control group (relative risk, 0.50; CI, 0.37-0.66; $P < .001$). Thus, SGLT2i are associated with a significant reduction in the risk of dementia in patients with T2D.[68]

In a meta-analysis of 11 clinical trials, the use of SGLT2i significantly reduced the risk of dementia compared with nonuse of SGLT2i (hazard ratio, 0.68; 95% CI, 0.50-0.92). In addition, SGLT2i use has a positive effect on cognitive function score improvement, as evidenced by the standardized mean difference of 0.88 (95% CI, 0.32-1.44), especially among populations with mild cognitive impairment or dementia.[69]

Thus, a several studies have shown the neuroprotective properties of SGLT2i, mainly associated with T2D. Fundamental mechanisms underlying the neuroprotective action of SGLT2i have also been proposed. However, further clinical studies of SGLT2i are needed to develop a personalized approach of SGLT2i administration to patients with or without T2D.

Conclusions

Upon analysis of the data presented in this article, it is noteworthy to mention the tendency of SGLT2i to exhibit hepatoprotective, neuroprotective, retinoprotective, and oncoprotective properties. However, the available evidence is promising but remains limited. Further research in this domain represents a pertinent multidisciplinary scope of interest with direct clinical implications.

Author contributions

Concept and design: All authors
Acquisition, analysis, or interpretation of data: All authors
Manuscript drafting: All authors
Manuscript revising: Pogosova, Urazova, Sarrafzadegan

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Конфликт интересов

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