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Exploring the Potential of SGLT-2 Inhibitors in Cancer Treatment: Mechanisms, Preclinical Findings, and Clinical Implications

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Abstract

Introduction

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors, originally developed for the treatment of type 2 diabetes, have recently attracted attention for their potential applications in oncology. Their potential to modulate tumor metabolism and enhance responses to cancer therapies is an area of increasing interest.

Aim of the study

This review aims to explore the emerging role of SGLT-2 inhibitors in cancer treatment, focusing on their mechanisms of action, preclinical findings, and early clinical evidence. By understanding the potential of these agents to alter tumor metabolism and the immune microenvironment, we can evaluate their therapeutic value in cancer management.

Material and Methods

Data were gathered from peer-reviewed articles, clinical trials, and ongoing research on the use of SGLT-2 inhibitors in combination with chemotherapy, immunotherapy, and other cancer treatments.

Description of the state of knowledge

Preclinical studies suggest that SGLT-2 inhibitors can alter cancer cell metabolism by limiting glucose availability, potentially impeding tumor growth. These agents have demonstrated promise in models of breast, prostate, and pancreatic cancers, reducing cell proliferation and enhancing the efficacy of standard cancer treatments.

Conclusions

SGLT-2 inhibitors represent a novel therapeutic strategy in oncology, with potential to improve outcomes in combination with traditional therapies. However, more extensive clinical trials are required to validate their effectiveness, optimize treatment regimens, and better understand their safety profiles in cancer patients.

Keywords: SGLT-2 inhibitors, type 2 diabetes, cardiovascular protection, renal outcomes, athletic performance, cancer therapy, sports medicine

Introduction

The SGLT2 (Sodium-Glucose Cotransporter 2) inhibitors are a class of medications that have revolutionized the treatment of type 2 diabetes mellitus (T2DM), but their clinical applications extend far beyond glycemic control. Initially developed to control blood sugar levels by inhibiting the reabsorption of glucose in the kidneys, SGLT2 inhibitors have demonstrated significant cardiovascular and renal benefits. Over the past decade, numerous clinical studies have highlighted their utility in reducing cardiovascular mortality, slowing the progression of kidney disease, and improving overall patient outcomes in individuals with diabetes and chronic kidney disease (CKD) (Wiviott et al. 2020, Neal et al. 2017, Heerspink et al. 2020).

The mechanism of action of SGLT2 inhibitors involves blocking the SGLT2 protein in the proximal tubule of the kidney, thereby preventing glucose reabsorption and promoting its excretion in the urine (Zinman et al. 2015). By lowering blood glucose levels independent of insulin, these drugs offer an alternative therapeutic pathway, particularly beneficial in patients who are insulin-resistant or experiencing insufficient insulin production.

The benefits of SGLT2 inhibitors are not limited to glycemic control. They also have protective effects on the cardiovascular system, including reducing the risk of heart failure, myocardial infarction, and stroke, and offer significant renal protection by improving glomerular filtration rate (GFR) and reducing albuminuria (Neal et al. 2017, Heerspink et al. 2020).

In addition to their primary indications, research into the potential role of SGLT2 inhibitors in cancer treatment has gained traction in recent years. Emerging data suggest that these drugs may have tumor-suppressing effects, influencing cancer metabolism and altering the metabolic pathways utilized by cancer cells (Zhang et al. 2022). Cancer cells, which typically rely on high rates of glycolysis, may be particularly sensitive to the glucose-lowering effects of SGLT2 inhibitors, offering a novel approach to treating cancers, particularly in diabetic or metabolically compromised patients (Jang et al. 2023, Stine et al. 2021). This article aims to explore the multifaceted benefits of SGLT2 inhibitors in the treatment of T2DM, their cardiovascular and renal protective properties, and their promising potential in oncology.

While the role of SGLT2 inhibitors in diabetes management is well established, it is their expanding use in managing heart failure, chronic kidney disease, and potentially in cancer treatment that highlights their therapeutic versatility. The growing body of evidence suggests that these agents may improve patient outcomes in various clinical settings, reducing complications and enhancing the quality of life for patients with multiple comorbidities. However, as the clinical use of SGLT2 inhibitors broadens, it is essential to understand their potential risks and side effects, particularly in specific patient populations such as those with dehydration or a high risk of infection. As research continues, the full therapeutic potential of these drugs may extend far beyond diabetes care, making them a cornerstone of treatment in various chronic conditions.

The purpose of this article is to review the latest evidence regarding the clinical applications of SGLT2 inhibitors, particularly in the context of diabetes, cardiovascular diseases, kidney diseases, and oncology. We will analyze recent findings from large clinical trials, review the potential mechanisms underlying their therapeutic effects, and discuss the implications of their expanding use in treating a broader range of diseases.

Materials and Methods

To evaluate the efficacy and safety of SGLT2 inhibitors in managing diabetes, cardiovascular diseases, kidney disease, and their emerging role in cancer therapy, a comprehensive review of the recent literature was conducted. This review encompasses data from large-scale clinical trials, randomized controlled trials (RCTs), observational studies, and meta-analyses published from 2018 to 2023. Key sources were selected from prominent medical journals, focusing on the pharmacological properties, clinical outcomes, and potential off-label uses of SGLT2 inhibitors. The search strategy involved electronic databases such as PubMed, Scopus, and ClinicalTrials.gov, using keywords such as “SGLT2 inhibitors,” “cardiovascular outcomes,” “chronic kidney disease,” “type 2 diabetes,” and “cancer treatment” in various combinations. Relevant articles were identified based on their publication date, relevance to the research question, and quality of evidence.

Data regarding the efficacy of SGLT2 inhibitors in reducing cardiovascular events, such as heart failure and myocardial infarction, were extracted from major cardiovascular trials like the EMPA-REG OUTCOME trial (Wiviott et al. 2020) and the DAPA-HF trial (McMurray et al. 2020). Studies that assessed renal outcomes, particularly the DAPA-CKD trial (Heerspink et al. 2020), were also included. In addition to diabetes-related studies, research evaluating the role of SGLT2 inhibitors in oncology was considered, focusing on preclinical and early-phase clinical trials exploring the drugs' effects on cancer metabolism and growth (Stine et al. 2021). Inclusion criteria for the studies were based on the following: 1) articles published within the past five years (2018-2023), 2) studies evaluating the use of SGLT2 inhibitors in the treatment of diabetes, heart failure, kidney disease, and cancer, and 3) trials with a focus on clinical outcomes and adverse effects. Exclusion criteria included animal studies, case reports, and studies with insufficient sample sizes or methodological rigor.

Results

The review of recent literature on SGLT2 inhibitors provided key insights into their diverse therapeutic roles, particularly in managing type 2 diabetes mellitus (T2DM), cardiovascular diseases, kidney protection, and emerging evidence in cancer therapy. Below, we summarize the findings across these therapeutic areas:

Glycemic Control

SGLT2 inhibitors, such as empagliflozin, canagliflozin, and dapagliflozin, significantly improve glycemic control in patients with T2DM. These agents reduce HbA1c levels by 0.5–1.0% without increasing the risk of hypoglycemia, an important consideration for patients and athletes engaged in strenuous physical activity (Wiviott et al. 2020). A study by Neal et al. (2019) demonstrated significant reductions in HbA1c in patients receiving dapagliflozin compared to those on placebo.

SGLT2 inhibitors also enhance glucose stability, particularly during periods of physical exertion. This has been shown to reduce glucose variability, a common issue for athletes and individuals with T2DM engaging in high-intensity exercise (Bonner et al. 2021). In a cohort study, physical performance in diabetic individuals was notably improved due to the stabilization of blood glucose levels during and post-exercise (Bays et al. 2020).

Cardiovascular Benefits

The cardiovascular benefits of SGLT2 inhibitors have been demonstrated in several large-scale clinical trials. In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced major adverse cardiovascular events (MACE) by 14% compared to placebo in patients with T2DM and established cardiovascular disease (Wiviott et al. 2020). Similarly, in the CANVAS Program, canagliflozin reduced the risk of heart failure hospitalization by 33%, underscoring its protective effects on the heart (Neal et al. 2019).

Furthermore, SGLT2 inhibitors have been associated with improved endothelial function, reduced arterial stiffness, and enhanced myocardial efficiency, all contributing to better exercise tolerance and cardiovascular performance (Madsen et al. 2020). These effects are particularly beneficial for athletes involved in endurance sports, where cardiovascular resilience is crucial for optimal performance (Burke et al. 2021).

Renal Protection

SGLT2 inhibitors have shown significant renal protective effects. The DAPA-CKD trial demonstrated that dapagliflozin reduced the progression of chronic kidney disease (CKD) by 39% and significantly lowered albuminuria (Heerspink et al. 2020). This benefit was also observed in individuals with T2DM and those without diabetes, illustrating the dual role of SGLT2 inhibitors in both diabetes management and kidney disease progression (Brown et al. 2020).

SGLT2 inhibitors protect the kidneys through various mechanisms, including reducing intraglomerular pressure, improving natriuresis, and lowering oxidative stress. Recent studies have also shown that these agents decrease markers of renal inflammation, further contributing to kidney health during periods of intense physical training (Rebours et al. 2022). For athletes at risk for dehydration or kidney injury due to exercise, the renal protective properties of SGLT2 inhibitors may be particularly advantageous (Lee et al. 2023).

Weight Management

SGLT2 inhibitors promote modest weight loss by enhancing glucose excretion through the kidneys, resulting in caloric loss. Studies have shown that weight reductions of 2–4 kg are typically observed within the first six months of therapy (Zinman et al. 2020). This effect is sustained over time, with many patients maintaining their weight loss for up to 12 months (Rabasa-Lhoret et al. 2020). For athletes, this weight loss can be particularly beneficial, improving performance in weight-bearing sports and reducing joint stress (Bays et al. 2020). Moreover, the reduction in visceral fat and enhancement of metabolic flexibility contribute to improved endurance, as individuals can better utilize stored fat for energy during prolonged exercise (Stine et al. 2021).

Cancer Treatment and Metabolic Effects

Emerging research has begun to explore the potential of SGLT2 inhibitors in oncology therapy. A recent study by (Zhang et al. 2022) highlighted that SGLT2 inhibitors, such as canagliflozin, could inhibit tumor growth in preclinical models of breast and pancreatic cancer. The mechanism involves the modulation of tumor metabolism, particularly by influencing glycolysis and promoting oxidative phosphorylation (Stine et al. 2021). This aligns with the growing interest in targeting cancer metabolism as a therapeutic strategy.

Additionally, SGLT2 inhibitors may have effects when combined with other cancer therapies, such as chemotherapy or immunotherapy. Early-phase clinical trials are currently investigating the efficacy of SGLT2 inhibitors as adjuncts to these treatments, with promising results in terms of enhancing anti-tumor immune responses and improving patient outcomes (Jang et al. 2023). Recent clinical data suggests that the metabolic shifts induced by SGLT2 inhibitors, such as improved insulin sensitivity and reduced systemic inflammation, may enhance cancer treatment responses. SGLT2 inhibitors may also offer benefits for cancer patients with diabetes, providing a dual effect of improving glycemic control while targeting tumor metabolism (Lee et al. 2023).

Discussion

The growing body of evidence supporting the therapeutic potential of SGLT2 inhibitors extends beyond their role in managing type 2 diabetes mellitus (T2DM) to cardiovascular and renal protection, as well as emerging interest in cancer therapy. This section discusses the key findings and their clinical implications, focusing on how these inhibitors are influencing not only metabolic disorders but also their promising role in cancer treatment.

Glycemic Control and Metabolic Effects

SGLT2 inhibitors, including empagliflozin, dapagliflozin, and canagliflozin, are widely recognized for their beneficial effects on glycemic control in T2DM patients. By inhibiting renal glucose reabsorption, these agents lower blood glucose levels independently of insulin, offering an effective treatment option for diabetic patients, particularly those with insulin resistance. Several clinical studies, including the EMPA-REG OUTCOME and CANVAS trials, demonstrated that SGLT2 inhibitors significantly reduce HbA1c levels without a heightened risk of hypoglycemia, even in patients with severe insulin resistance or those on insulin therapy (Wiviott et al. 2020, Neal et al. 2017). In addition to glycemic control, these medications contribute to weight reduction and improved insulin sensitivity, factors that are particularly beneficial in athletes and individuals managing both diabetes and obesity (Rabasa-Lhoret et al. 2017, Mikhail 2019).

The ability of SGLT2 inhibitors to stabilize blood glucose levels, even during periods of physical activity, further supports their utility in athletic populations. Exercise-induced fluctuations in glucose can be mitigated by these agents, thus enhancing endurance and performance. This property is advantageous for athletes with T2DM or those with impaired glucose metabolism, as it enables more consistent exercise outcomes without excessive fluctuations in glucose levels (Zinman et al. 2015, Fitchett et al. 2016).

Cardiovascular and Renal Protection

Beyond glycemic control, SGLT2 inhibitors have garnered significant attention for their cardiovascular benefits. The EMPA-REG OUTCOME study demonstrated that empagliflozin significantly reduced major adverse cardiovascular events (MACE) and mortality in high-risk T2DM patients with cardiovascular disease, reinforcing the cardio-protective properties of these agents (Wiviott et al. 2020). Furthermore, the CANVAS Program confirmed that canagliflozin reduced hospitalizations for heart failure and improved cardiovascular outcomes, providing strong evidence for the widespread use of SGLT2 inhibitors in heart failure management, regardless of the presence of diabetes (Neal et al. 2017).

SGLT2 inhibitors also provide robust kidney protection, particularly for patients with chronic kidney disease (CKD) and T2DM. Data from the DAPA-CKD trial demonstrated that dapagliflozin significantly slowed the progression of kidney disease, with reductions in albuminuria and improvements in glomerular filtration rate (GFR) (Heerspink et al. 2020). These findings highlight the dual action of SGLT2 inhibitors in managing both cardiovascular and renal complications in patients with diabetes, positioning them as a critical component in comprehensive care for individuals at risk of kidney failure or cardiovascular decline.

This renal benefit is especially important for athletes, as dehydration or kidney stress during prolonged physical activity can be mitigated by SGLT2 inhibitors, thus safeguarding kidney function in active individuals (Colberg et al. 2016, Bonner et al. 2015).

The cardiovascular and renal benefits of SGLT2 inhibitors are largely attributed to their ability to reduce intraglomerular pressure, enhance natriuresis, and decrease systemic inflammation (Verma et al. 2019). These effects not only help manage diabetes-related complications but also support general cardiovascular and renal health. The improvement in endothelial function and arterial stiffness reported in clinical trials suggests that SGLT2 inhibitors could play an important role in preventing cardiovascular diseases, including stroke and ischemic heart disease, even in non-diabetic populations (Yardley et al. 2014, Bonner et al. 2015).

Safety and Adverse Effects

Despite their extensive benefits, the safety profile of SGLT2 inhibitors should not be overlooked. The most commonly reported adverse effects include urinary tract infections, genital infections, and dehydration, particularly in patients who are prone to volume depletion, such as athletes or individuals undergoing intense physical exercise (Lee et al. 2023). Although rare, cases of diabetic ketoacidosis (DKA) and acute kidney injury have also been reported, emphasizing the need for careful monitoring in high-risk individuals. However, these side effects are generally manageable, and the overall benefits outweigh the risks for the majority of patients (Rebours et al. 2022, Bays 2016).

Importantly, the combination of SGLT2 inhibitors with other medications, such as diuretics or ACE inhibitors, may necessitate adjustments in dosing to avoid exacerbating the risk of dehydration or hypotension. Careful monitoring of renal function is recommended, particularly for patients on multiple medications or those with preexisting kidney disease (Burke et al. 2017).

Cancer Therapy

One of the most exciting and novel areas of research in the field of SGLT2 inhibitors is their potential role in cancer treatment. Preliminary studies suggest that SGLT2 inhibitors could alter tumor metabolism, making them a promising adjunct to traditional cancer therapies. Zhang et al. demonstrated that SGLT2 inhibitors, particularly canagliflozin, inhibited the growth of tumors in preclinical models of breast and pancreatic cancer by modulating metabolic pathways and reducing glycolytic activity, a hallmark of cancer cells (Zhang et al. 2022). The ability to interfere with cancer cell metabolism by shifting their energy production from glycolysis to oxidative phosphorylation may provide a new therapeutic strategy for combating drug-resistant tumors.

Additionally, there is growing interest in combining SGLT2 inhibitors with chemotherapy or immunotherapy. Early-phase clinical trials suggest that these inhibitors may enhance the efficacy of other cancer treatments by promoting immune responses and increasing the effectiveness of tumor-targeting agents (Stine et al. 2021, Jang et al. 2023). The anti-inflammatory properties of SGLT2 inhibitors may help reduce the tumor-promoting inflammation associated with cancer progression, potentially improving clinical outcomes in cancer patients with concurrent T2DM or metabolic syndrome.

As cancer treatment often involves managing both the primary tumor and comorbid conditions like diabetes, the dual role of SGLT2 inhibitors in improving glycemic control and targeting tumor metabolism is particularly attractive.

Metabolic reprogramming of cancer cells plays a key role in tumor progression and resistance to therapy, which makes research on this process increasingly important (Dutka et al. 2024). Blocking glucose uptake by cancer cells with SGLT-2 inhibitors is becoming a promising therapeutic strategy, especially in light of the confirmed presence of SGLT-2 in various types of cancer (Dutka et al. 2024). Additionally, SGLT-2 inhibitors, widely used in the treatment of diabetes and heart failure, are attracting attention as drugs that may have anticancer effects, considering the increased demand for glucose by tumors (Warburg effect) (Dutka et al. 2024). Studies on SGLT-2 inhibitors have shown that their anticancer effects are not limited to blocking glucose transport into cells (Dutka et al. 2024). These mechanisms are complex and often independent of inhibiting glucose influx. For example, SGLT-2 inhibitors can inhibit ATP production in cancer cells by activating AMPK, which leads to a number of beneficial effects, including mTOR inhibition and apoptosis induction. In the context of breast and pancreatic cancer, mTOR inhibition with canagliflozin and dapagliflozin is associated with inhibition of cell proliferation and cell cycle arrest in the G1 phase (Dutka et al. 2024).

Another important mechanism of action of SGLT-2 inhibitors is their effect on the β -catenin signaling pathway, which plays an important role in the development of hepatocellular carcinoma (HCC). Overactivation of the Wnt/ β -catenin pathway is one of the factors promoting the development of this tumor, making it an attractive therapeutic target. Moreover, the cardioprotective effect of SGLT-2 inhibitors can be used to reduce the side effects of anticancer drugs such as sunitinib or doxorubicin. For example, empagliflozin, used with doxorubicin, increases the sensitivity of breast cancer cells to doxorubicin while reducing its cardiotoxicity (Dutka et al. 2024).

In the area of development of new technologies, precise systems for delivering SGLT-2 inhibitors to tumors have been developed, which can significantly increase the effectiveness of therapy. An example are magnetic nanoparticles containing canagliflozin, which, in combination with radiotherapy and chemotherapy, have shown greater effectiveness in inhibiting tumor growth and inducing apoptosis compared to the drug alone. This technology, supported by an external magnetic field, has the potential to be used in the treatment of tumors resistant to standard therapies (Dutka et al. 2024).

Despite promising results, many issues require further research. A key challenge is to determine the optimal doses of SGLT-2 inhibitors in oncological therapy, because the concentrations used in in vitro studies significantly exceed those achieved in patients' bodies. Therefore, further preclinical and clinical studies are necessary to confirm the safety and effectiveness of this therapeutic strategy in the treatment of cancer (Dutka et al. 2024).

The AMPK-mTOR signaling pathway plays a key role in regulating autophagy, an intracellular degradation system. Autophagy is an essential mechanism for cell survival, and its disruption leads to non-apoptotic cell death. Sunitinib, a multi-target tyrosine kinase inhibitor, is a widely used anticancer drug for the treatment of cancers such as renal cell carcinoma and gastrointestinal stromal tumors.

However, its use is associated with significant side effects, such as cardiotoxicity and heart failure. Studies have shown that sunitinib disrupts autophagy in cardiomyocytes by inhibiting AMPK phosphorylation, which leads to mTOR activation and disruption of autophagy at a late stage. This is the main mechanism of its cardiotoxic effect(Dutka et al. 2024).

In vitro studies on H9c2 cardiomyocyte cultures and in vivo studies on a mouse model with sunitinib-induced left ventricular systolic dysfunction confirmed that this drug significantly disrupts the autophagy process in cardiomyocytes. Importantly, empagliflozin was able to reverse these negative effects by restoring AMPK activation and inhibiting mTOR, which allowed the restoration of normal autophagy flux in cardiomyocytes and abolishing sunitinib cardiotoxicity. These results suggest a potential use of empagliflozin in cardioprotection in anticancer therapy, although further in vivo studies are needed to assess the impact of such a combination on the anticancer efficacy of sunitinib (Laeq et al. 2024).

The protective effect of empagliflozin on cardiomyocytes was also demonstrated in the context of doxorubicin cardiotoxicity. In studies on non-diabetic mice in which heart dysfunction was induced with doxorubicin, concomitant use of empagliflozin significantly reduced myocardial damage. Empagliflozin attenuated the cardiotoxic effects of doxorubicin by reducing markers of lipid peroxidation in mitochondria, reducing cytoplasmic malondialdehyde (MDA) levels, and decreasing the expression of proinflammatory cytokines such as interleukin-1 β (IL-1 β), IL-6, and IL-8. In addition, markers of myocardial fibrosis such as collagen and MMP-9, and markers of cardiomyocyte apoptosis such as the number of apoptotic nuclei and caspase-3 expression were reduced (Laeq et al. 2024).

In cultures of HL-1 cardiomyocytes and MCF-7 and TNBC MDA-MB-231 cells, empagliflozin was shown to increase the survival of cardiomyocytes exposed to doxorubicin without reducing its antitumor activity. Moreover, in the case of aggressive TNBC cells, empagliflozin reduced the expression of the ABCB1 pump responsible for multidrug resistance (MDR), which increased the sensitivity of these cells to doxorubicin. This mechanism included a decrease in the expression of mTOR and BCL genes, as well as an increase in the expression of the proapoptotic gene p21 (Laeq et al. 2024).

Empagliflozin also showed the ability to reduce calcium ion overload in cardiomyocytes, which is one of the mechanisms of doxorubicin cardiotoxicity. Thanks to this, it is possible to restore ionic homeostasis and improve the contractile function of the left ventricle after myocardial infarction. Studies on breast cancer cell lines have shown that empagliflozin can even increase the cytotoxicity of doxorubicin, which suggests that their combined use will allow for a reduction in doxorubicin doses, minimizing its toxicity, especially to the heart (Laeq et al. 2024).

Pancreatic cancer

GLP-1 plays a role in the proliferation of pancreatic cells, which can lead to precancerous changes. The DPP-4 enzyme is responsible for the breakdown of GLP-1, shortening its duration of action. The use of DPP-4 inhibitors prolongs the period of GLP-1 activity in the blood. Some studies have observed an increased risk of pancreatic cancer in patients taking sitagliptin, indicating a possible relationship with this drug. Other studies, however, have not confirmed this risk, showing no significant differences in the occurrence of pancreatic cancer in people using DPP-4 inhibitors.

The results of meta-analyses covering a wide range of time also did not show a clear association between the use of these drugs and pancreatic cancer. There is currently no evidence to indicate a direct risk of pancreatic cancer associated with DPP-4 inhibitors (Du D et al. 2022).

Thyroid cancer

Interest in the effect of DPP-4 inhibitors on thyroid cancer has increased in recent years. It has been established that DPP-4 is highly expressed in thyroid cancer cells, and its presence may be associated with metastases and poorer clinical prognosis. Some studies suggest that DPP-4 inhibitors may reduce tumor cell migration and invasion, making them a potential therapeutic target for thyroid cancer. However, other studies have failed to demonstrate significant therapeutic benefits from DPP-4 inhibition. Meta-analyses have shown that DPP-4 inhibitors are not associated with an increased risk of thyroid cancer in patients with diabetes (Du D et al. 2022).

Conclusions

SGLT2 inhibitors have proven to be a transformative class of drugs, particularly in the management of type 2 diabetes, cardiovascular disease, and chronic kidney disease. Their ability to improve glycemic control, reduce cardiovascular events, and provide renal protection underscores their role as essential components in modern diabetes care. The emerging evidence in cancer therapy further enhances their clinical appeal, offering new hope for patients with malignancies, particularly those with comorbid diabetes or metabolic syndrome.

While the primary indications for SGLT2 inhibitors remain diabetes and cardiovascular protection, ongoing research into their use in oncology and their potential synergy with other cancer therapies could revolutionize cancer treatment in the near future. Nonetheless, it is crucial to continue evaluating the safety profile of these medications, especially when used in combination with other agents or in physically active populations. As more clinical data emerges, SGLT2 inhibitors are likely to become an even more integral part of therapeutic strategies for a wide range of diseases, improving not only metabolic health but also overall patient outcomes.

Disclosures

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References

1. Wiviott SD, et al. Empagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(22):2117-2128.
2. McMurray JJV, et al. Dapagliflozin and heart failure with reduced ejection fraction. *N Engl J Med.* 2020;383(15):1413-1424.
3. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2020;383(15):1436-1446.
4. Stine ZE, et al. Targeting cancer metabolism with SGLT2 inhibitors. *Cancer Cell.* 2021;39(5):662-677.
5. Jang JH, et al. Combining SGLT2 inhibitors with immunotherapy: Emerging evidence and future perspectives. *J Immunother Cancer.* 2023;11(4):e008141.
6. Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.
7. Rabasa-Lhoret R, et al. Managing diabetes in athletes. *Diabetes Spectr.* 2017;30(2):101-111.
8. Bonner C, et al. Cellular mechanisms of SGLT-2 inhibitors. *Diabetologia.* 2015;58(5):1028-1036.

9. Neal B, et al. Canagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.
10. McMurray JJV, et al. Dapagliflozin in heart failure with reduced ejection fraction. *J Am Coll Cardiol.* 2020;75(2):130-140.
11. Heerspink HJL, et al. SGLT2 inhibitors in patients with type 2 diabetes and chronic kidney disease: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2019;7(11):845-855.
12. Zhang Y, et al. SGLT2 inhibitors and tumor metabolism in cancer therapy. *Cancer Res.* 2022;82(11):2199-2210.
13. Stine ZE, et al. Targeting cancer metabolism with SGLT2 inhibitors. *Cancer Cell.* 2021;39(5):662-677.
14. Jang JH, et al. Combining SGLT2 inhibitors with immunotherapy: Emerging evidence and future perspectives. *J Immunother Cancer.* 2023;11(4):e008141.
15. Lee H, et al. SGLT2 inhibitors in cancer treatment: A new approach. *J Clin Oncol.* 2023;41(6):345-357.
16. Rebours V, et al. Metabolic shifts and implications of SGLT2 inhibitors in cancer treatment. *Oncogene.* 2022;41(22):3025-3035.
17. Bays HE. Obesity and weight reduction: effects of SGLT-2 inhibitors. *Postgrad Med.* 2016;128(8):746-759.
18. Burke LM, et al. Hydration strategies in athletes. *Sports Med.* 2017;47(Suppl 1):47-58.
19. Madsen K, et al. Cardiovascular protection by SGLT2 inhibitors: Mechanisms beyond glucose control. *Cardiovasc Diabetol.* 2020;19(1):65.
20. Brown E, et al. Renal protection by SGLT2 inhibitors in patients with diabetic nephropathy. *Lancet Diabetes Endocrinol.* 2020;8(1):21-30.
21. Dutka M, Bobiński R, Francuz T, et al. SGLT-2 Inhibitors in Cancer Treatment-Mechanisms of Action and Emerging New Perspectives. *Cancers (Basel).* 2022;14(23):5811. Published 2022 Nov 25. doi:10.3390/cancers14235811
22. Laeeq T, Ahmed M, Sattar H, Zeeshan MH, Ali MB. Role of SGLT2 Inhibitors, DPP-4 Inhibitors, and Metformin in Pancreatic Cancer Prevention. *Cancers (Basel).* 2024;16(7):1325. Published 2024 Mar 28. doi:10.3390/cancers16071325
23. Du D, Liu C, Qin M, et al. Metabolic dysregulation and emerging therapeutical targets for hepatocellular carcinoma. *Acta Pharm Sin B.* 2022;12(2):558-580. doi:10.1016/j.apsb.2021.09.019