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Possible amelioration impact of sodium-glucose cotransporter 2 inhibitors on cisplatin-induced renal toxicity; a mini-review on recent findings

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ABSTRACT

Cisplatin-induced nephrotoxicity is a crucial concern in cancer patients, limiting the dose and duration of cisplatin therapy. Several mechanisms contribute to cisplatin nephrotoxicity, including oxidative stress, inflammation, and mitochondrial dysfunction. SGLT2 inhibitors have emerged as a promising therapeutic option for various renal disorders due to their ability to restore renal homeostasis and mitigate renal injury.

Keywords: Cisplatin-induced nephrotoxicity, Sodium-glucose cotransporter 2 inhibitors, Oxidative stress, Inflammation, Mitochondrial dysfunction, Acute kidney injury, Chronic kidney disease, Empagliflozin, Renoprotection

Mini-Review

Implication for health policy/practice/research/medical education:
Cisplatin is a broadly administered chemotherapeutic compound for the treatment of several solid tumors; though, its use is frequently limited due to the development of nephrotoxicity. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of drugs utilized to treat type 2 diabetes by inhibiting the SGLT2 accountable for glucose reabsorption in the kidneys. These inhibitors have also shown promise in improving renal function following administration of cisplatin, a commonly used chemotherapeutic drug that can cause kidney damage.

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Introduction

Cisplatin is a widely used chemotherapy drug that is effective against a variety of cancers. However, its administration is limited due to its nephrotoxicity, which can lead to acute renal damage and chronic renal failure (1). Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of drugs used to treat type 2 diabetes mellitus (T2DM) by blocking glucose reabsorption in the kidneys. In recent years, SGLT2 inhibitors have been shown to have potential in reducing cisplatin-induced nephrotoxicity (2-4).

Numerous studies have determined the beneficial effects of SGLT2 inhibitors in reducing cisplatin-induced nephrotoxicity. These drugs have been disclosed to improve renal function, diminish oxidative stress, and decrease inflammation. Additionally, SGLT2 inhibitors have been shown to reduce the accumulation of cisplatin in the kidneys, which is thought to be one of the main mechanisms of cisplatin-induced nephrotoxicity (5,6).

A previous experimental study showed that treatment with the SGLT2 inhibitor empagliflozin significantly reduced cisplatin-induced acute kidney injury (AKI). The study found that empagliflozin treatment reduced oxidative stress and inflammation in the kidneys, as well as reducing the expression of genes associated with renal fibrosis (7).

Protective effects of SGLT2 inhibitor dapagliflozin on renal function and reduced the incidence of AKI was also detected in other studies. Hence, SGLT2 inhibitors have shown promising renoprotective effects in preclinical and clinical studies evaluating cisplatin-induced nephrotoxicity (5,8-10). This mini-review sought to identify relevant studies investigating the administration of SGLT2 inhibitors in cisplatin nephrotoxicity.

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Search strategy

For this review, we conducted a comprehensive search of various databases including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase. We used different keywords such as cisplatin-induced nephrotoxicity, sodium-glucose cotransporter 2 inhibitors, oxidative stress, inflammation, mitochondrial dysfunction, acute kidney injury, chronic kidney disease, acute renal failure, empagliflozin, SGLT2 inhibitors and renoprotection.

Morphologic lesions of cisplatin-induced renal toxicity

Cisplatin nephrotoxicity can lead to the loss of renal function, ultimately resulting in acute renal failure. Cisplatin accumulation in renal cells can cause damage to the kidney tubules, running to shedding and necrosis of the tubular epithelial cells (1). Cisplatin-induced nephrotoxicity is characterized by a decrease in renal blood flow and glomerular filtration rate. The accumulation and retention of cisplatin in renal cells can lead to DNA damage, oxidative stress, apoptosis, and autophagy. Cisplatin-induced nephrotoxicity can result in ischemia or necrosis of the proximal renal tubular epithelial cells (11). Cisplatin can cause damage to the kidney tubules, directing to shedding and necrosis of the tubular epithelial cells. Cisplatin-induced nephrotoxicity can result in glomerular injury, including glomerular sclerosis and mesangial cell proliferation. Inflammatory infiltrates in the renal interstitium can be observed in cisplatin-induced nephrotoxicity. Prolonged exposure to cisplatin can lead to the development of renal fibrosis, characterized by the accumulation of extracellular matrix components (1,12). Cisplatin can cause vascular changes in the kidneys, including endothelial cell injury and thrombotic microangiopathy. These morphologic lesions contribute to the development of acute renal failure and the impairment of renal function in cisplatin-treated patients. Clinically, these morphologic lesions contribute to the extension of acute renal failure and the impairment of renal function in cisplatin-treated patients (1,13).

A short look to the renoprotective strategies to prevent cisplatin-induced renal toxicity

These renoprotective strategies have shown potential in preventing cisplatin-induced renal toxicity. Adequate hydration is recommended to prevent cisplatin-induced nephrotoxicity by increasing urine flow and reducing the concentration of cisplatin in the kidneys. Magnesium supplementation has been shown to reduce cisplatin-induced nephrotoxicity by reducing oxidative stress and inflammation (12,14). Mannitol has been shown to reduce cisplatin-induced nephrotoxicity by increasing renal blood flow and reducing the concentration of cisplatin in the kidneys. Antioxidants like vitamin E and N-acetylcysteine have been shown to reduce cisplatin-induced nephrotoxicity by reducing oxidative stress and inflammation. Renoprotective agents such as erythropoietin and angiotensin-converting enzyme inhibitors have been shown to reduce cisplatin-induced nephrotoxicity by reducing inflammation and oxidative stress (15). Mesenchymal stem cells have been detected to have renoprotective properties in cisplatin-induced nephrotoxicity by reducing inflammation and oxidative stress. Anti-inflammatory agents such as dexamethasone have been shown to reduce cisplatin-induced nephrotoxicity by reducing inflammation. Inhibition of PKCδ has been shown to reduce cisplatin-induced nephrotoxicity without blocking chemotherapeutic efficacy in mouse models of cancer (16,17).

Recently, SGLT2 inhibitors have been studied for their potential role in the treatment of acute renal failure. SGLT2 inhibitors exert a variety of effects on the kidney, directly and indirectly linked to reduced glucose reabsorption, providing acute and chronic renal protection (18,19). The considerable meta-analysis and post hoc investigations have failed to realize a correlation amid SGLT2 inhibitors and acute renal failure (20). On the contrary, a possibly protective efficacy has been proposed (19). A pharmacovigilance study evaluated SGLT2 inhibitor-related AKI and found that pharmacoepidemiology studies are needed to compare the adverse events in different SGLT2 inhibitors (21). A clinical trial called PREVENTS-AKI is currently underway to investigate the potential of SGLT2 inhibitors to prevent AKI in intensive care patients (22).

There have been concerns grown concerning the risk for acute renal failure with SGLT2 inhibitors, particularly in patients with predisposing factors such as hypovolemia. SGLT2 inhibitors may contribute to acute renal failure by inducing volume depletion because of their natriuretic and osmotic efficacies, particularly in cases with predisposing factors such as hypovolemia (23). Additionally, the volume and intra-renal hemodynamic impacts of these agents may be synergistic when combined with frequently prescribed renin-angiotensin-aldosterone system (RAAS) antagonists and traditional diuretics in cases with type 2 diabetes and can deteriorate renal function (23,24).

Canagliflozin, an SGLT2 inhibitor, has emerged as a promising therapeutic agent in the management of T2DM. In addition to its well-established glycemic control effects, recent research has suggested that canagliflozin may offer potential renal protection benefits (25,26). Mechanisms underlying the potential renal protection by canagliflozin primarily involve hemodynamic effects, reduction in tubulointerstitial inflammation and fibrosis, reduction in oxidative stress, and modulation of local RAAS activity (19). Multiple clinical trials, including the CANVAS (CANagliflozin CardioVascular Assessment Study) program, have demonstrated significant reductions in albuminuria, decline in renal function, and a lower risk of adverse renal outcomes in patients with T2DM treated with canagliflozin (27-29). The renal protective effects of

canagliflozin are likely multifactorial, with contributions from both hemodynamic and direct tubuloprotective mechanisms. The reduction of glomerular hyperfiltration and improvement in intraglomerular perfusion, coupled with the attenuation of tubulointerstitial fibrosis and inflammation, may collectively contribute to the observed renal benefits (30,31). These effects could be mediated by various factors, including glucose-independent effects and RAAS modulation. Notably, recent evidence suggests that canagliflozin may provide renal benefits beyond its glucose-lowering effects, making it a promising therapeutic option in cisplatin-induced nephrotoxicity management (18,32).

Conclusion

The mechanism by which SGLT2 inhibitors ameliorate cisplatin nephrotoxicity appears that the inhibition of SGLT2 leads to increased glucose excretion, resulting in a shift towards fatty acid oxidation as an energy source in the kidney, which may contribute to cellular protection. Additionally, SGLT2 inhibitors have been shown to improve renal hemodynamics and reduce renal fibrosis, further supporting their renoprotective effects.

Authors' contribution

Conceptualization: Parisa Keshtgar, Samin Karamian, Leila Mahmoodnia.
Data curation: Parisa Keshtgar, Samin Karamian.
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Writing–review and editing: Parisa Keshtgar, Samin Karamian, Leila Mahmoodnia.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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