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SGLT2 inhibitors for the treatment of pulmonary hypertension; new trends

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ABSTRACT

The landscape of pulmonary hypertension (PAH) treatment is evolving, with SGLT2 inhibitors being recognized as a potential fourth treatment pathway alongside traditional therapies. Their incorporation into treatment strategies for PAH could represent a significant shift in management approaches.

Keywords: SGLT2 inhibitors, Pulmonary hypertension, Inflammation, Oxidative stress

Mini-Review

Implication for health policy/practice/research/medical education:
Sodium-glucose co-transporter 2 (SGLT2) inhibitors show promise in treating pulmonary hypertension (PAH) through their multifaceted effects on metabolism, vascular function, and hemodynamics.

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Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors, primarily developed for managing diabetes, are gaining attention for their potential role in treating pulmonary arterial hypertension (1). These agents could improve overall cardiovascular health too (2). The SGLT2 inhibitors can lead to vasodilation of pulmonary arteries. For instance, in a diabetic mouse model, both nonspecific and SGLT2-specific inhibitors demonstrated this effect, suggesting a direct impact on pulmonary vascular resistance (1,3,4). These compounds also reduce inflammation and prevent cardiac remodeling, which are critical factors in the progression of pulmonary hypertension (PAH) (1). Evidence indicates that SGLT2 inhibitors can ameliorate vascular remodeling in animal models of pulmonary arterial hypertension, potentially translating to improved outcomes in human patients (1,5). Prior studies also showed, that by enhancing cardiac output, SGLT2 inhibitors can alleviate congestion and secondary PAH (6). A study showed that the initiation of SGLT2 inhibitors in patients with heart failure resulted in significant reductions in pulmonary artery pressures over time, indicating improved hemodynamics (2,6). SGLT2 inhibitors promote diuresis by inhibiting glucose and sodium reabsorption in the kidneys. This action can lead to a reduction in blood volume, thereby decreasing the preload on the heart and reducing pulmonary artery pressures (7). This mechanism is particularly beneficial in patients with heart failure, where fluid overload is a common issue (7). SGLT2 inhibitors may reduce oxidative stress, which is implicated in the pathogenesis of PAH (1). By decreasing oxidative stress levels, these drugs can help protect pulmonary endothelial cells and improve overall vascular function (8). SGLT2 inhibitors also address metabolic dysfunction, which is increasingly recognized as a contributor to PAH. By improving metabolic parameters, these medications can positively influence pulmonary vascular health (1). Here we sought to take a short look at the role of SGLT2 inhibitors in the treatment of PAH.

Search strategy

For this review, we conducted a search across several databases, including PubMed, Web of Science, EBSCO, Scopus, Google Scholar, the Directory of Open Access Journals (DOAJ), and Embase. We utilized various keywords such as SGLT2 inhibitors, pulmonary hypertension, inflammation, and oxidative stress.

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Endothelial dysfunction in PAH

Endothelial dysfunction is a hallmark of PAH, characterized by impaired vasodilation, increased vasoconstriction, and vascular remodeling (9). This condition leads to elevated pulmonary vascular resistance and pressure, right heart failure, and increased mortality in PAH patients. SGLT2 inhibitors enhance endothelial nitric oxide (NO) production, leading to improved vasodilation of pulmonary arteries (1). These drugs attenuate inflammation, which is a key driver of endothelial dysfunction and vascular remodeling in PAH. SGLT2 inhibitors reduce oxidative stress, which contributes to endothelial injury and dysfunction (10). These agents improve mitochondrial homeostasis and increase endothelial cell survival. SGLT2 inhibitors promote the growth of new blood vessels, potentially improving endothelial function and pulmonary perfusion (10,11). SGLT2 inhibitors enhance mitochondrial homeostasis, which is crucial for endothelial cell survival and function. Improved mitochondrial function can lead to better energy production and reduced apoptosis in endothelial cells, thereby supporting their integrity (1,9,11). SGLT2 inhibitors have been shown to restore the integrity of the endothelial barrier, which is often compromised in PAH. This restoration can prevent leakage and maintain proper vascular function (12).

Clinical and experimental studies

While the administration of SGLT2 inhibitors in PAH is still an emerging area, several small-scale studies have reported promising results. For example, in animal studies, empagliflozin has been shown to reduce mortality and prevent progression in experimental models of PAH (1). Meanwhile, the EMBRACE-HF clinical trial showed that empagliflozin can significantly reduce pulmonary artery diastolic pressure in heart failure patients, suggesting a direct impact on pulmonary hemodynamics (13). Another randomized controlled trial indicated that dapagliflozin could attenuate the development of exercise-induced PH in patients with stable ischemic heart disease and preserved ejection fraction (14). However, despite these encouraging findings, further large-scale clinical trials are necessary to validate the efficacy of SGLT2 inhibitors in pulmonary arterial hypertension and to explore their integration into existing treatment regimens (15).

Conclusion

Emerging clinical evidence suggests that SGLT2 inhibitors, such as empagliflozin and dapagliflozin, can lead to improvements in pulmonary artery pressure and functional outcomes in patients with heart failure and associated PAH, which may be partly due to the anti-inflammatory effects of these agents.

Authors' contribution

Conceptualization: Rahimeh Eskandarian.
Data curation: Mohammad Memaria.
Investigation: Rahimeh Eskandarian, Mohammad Memaria.
Resources: Rahimeh Eskandarian.
Supervision: Rahimeh Eskandarian.
Validation: Rahimeh Eskandarian.
Visualization: Rahimeh Eskandarian.
Writing–original draft: Rahimeh Eskandarian.
Writing–review and editing: Rahimeh Eskandarian, Mohammad Memaria.

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.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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