Beyond diabetes: the role of SGLT2 inhibitors in modulating oxidative stress in nephrology.

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Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized the management of type 2 diabetes by reducing blood glucose levels through renal glucose excretion. However, emerging evidence suggests that their benefits extend beyond glycemic control. In recent years, SGLT2 inhibitors have gained attention for their nephroprotective properties, particularly through the modulation of oxidative stress. Chronic kidney disease (CKD) and other renal disorders are closely linked to oxidative damage, which contributes to inflammation, fibrosis, and progression of kidney dysfunction. This article explores the potential of SGLT2 inhibitors in oxidative stress modulation and their impact on nephrology [1].

Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defense mechanisms. In the kidneys, excessive oxidative stress can lead to endothelial dysfunction, mitochondrial damage, and increased inflammation, all of which contribute to renal disease progression. Patients with diabetes and CKD often exhibit high oxidative stress levels, exacerbating renal impairment and cardiovascular complications. Targeting oxidative stress has become a critical strategy in slowing kidney disease progression [2].

SGLT2 inhibitors, such as empagliflozin, dapagliflozin, and canagliflozin, were initially developed as antihyperglycemic agents. However, clinical trials, including EMPA-REG OUTCOME, CREDENCE, and DAPA-CKD, have demonstrated their renoprotective effects independent of glucose lowering. These benefits include reduced albuminuria, preservation of glomerular filtration rate (GFR), and decreased risk of CKD progression. Notably, the antioxidant properties of SGLT2 inhibitors play a crucial role in these protective mechanisms [3].

SGLT2 inhibitors contribute to oxidative stress modulation through several mechanisms. First, they reduce mitochondrial dysfunction by lowering ROS production, thereby preserving cellular energy metabolism in renal cells. Second, these inhibitors enhance autophagy, a process that removes damaged cellular components and maintains kidney homeostasis. Third, SGLT2 inhibition reduces inflammation and fibrosis by downregulating pro-inflammatory cytokines and oxidative stress-related signaling pathways, such as the nuclear factor-kappa B (NF-κB) and NLRP3 inflammasome [4].

Mitochondria are vital for energy production in renal tubular cells, but they are also primary sources of oxidative stress. SGLT2 inhibitors improve mitochondrial efficiency by reducing ROS generation and promoting adaptive responses such as increased mitochondrial biogenesis and improved electron transport chain function. This mitochondrial protection contributes to the overall improvement in renal function and slows disease progression [5].

Another critical aspect of SGLT2 inhibitors' nephroprotective effects is their ability to improve renal hemodynamics. These drugs reduce intraglomerular pressure by promoting afferent arteriolar vasoconstriction and efferent arteriolar vasodilation. This hemodynamic shift decreases oxidative stress-induced damage to glomerular cells, reducing proteinuria and slowing the progression of CKD [6].

Chronic inflammation is a hallmark of CKD, driven in part by oxidative stress. SGLT2 inhibitors exhibit anti-inflammatory properties by lowering levels of pro-inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). This reduction in systemic inflammation not only benefits kidney health but also decreases the risk of cardiovascular events commonly associated with CKD [7].

Beyond their direct effects on oxidative stress, SGLT2 inhibitors provide substantial cardiovascular benefits, which are closely linked to renal protection. By reducing oxidative stress, these drugs lower the risk of atherosclerosis, heart failure, and hypertension common comorbidities in CKD patients. The cardiovascular and renal protective synergy further strengthens the case for SGLT2 inhibitors in nephrology beyond their traditional role in diabetes management [8].

The expanding role of SGLT2 inhibitors in nephrology suggests that these drugs could be utilized in a broader patient population, including non-diabetic CKD patients. Ongoing research aims to explore their full potential in oxidative stress modulation and renal protection. Future studies will help determine optimal patient selection, dosing strategies, and long-term outcomes to maximize their therapeutic benefits [9, 10].

Conclusion

SGLT2 inhibitors have emerged as more than just glucose-lowering agents; they represent a promising therapeutic approach in nephrology, particularly through oxidative stress modulation. By improving mitochondrial function, reducing inflammation, and preserving renal function, these drugs offer

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***Received:** 2-Feb-2025, Manuscript No. AACNT-25-161913; **Editor assigned:** 3-Feb-2025, PreQC No. AACNT-25-161913(PQ); **Reviewed:** 16-Feb-2025, QC No. AACNT-25-161913; **Revised:** 20-Feb-2025, Manuscript No. AACNT-25-161913(R); **Published:** 27-Feb-2025, DOI: 10.35841/aacnt-9.1.250*

***Citation:** Gilbert S. Beyond diabetes: the role of SGLT2 inhibitors in modulating oxidative stress in nephrology. J Clin Nephrol. 2025; 9(1):250.*

hope for patients with CKD and other renal disorders. As research continues to uncover new benefits, SGLT2 inhibitors may become a cornerstone therapy in nephrology, extending their impact far beyond diabetes management.

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Citation: *Gilbert S. Beyond diabetes: the role of SGLT2 inhibitors in modulating oxidative stress in nephrology. J Clini Nephrol. 2025; 9(1):250.*