The Impact of SGLT2 Inhibitors on The Progression of Chronic Kidney Disease

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ABSTRACT

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Introduction: Chronic Kidney Disease (CKD) is a progressive condition leading to significant morbidity and mortality. Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, originally for type 2 diabetes, have shown significant benefits in slowing CKD progression, regardless of diabetes status. This review summarizes the mechanisms and clinical impact of SGLT2 inhibitors on CKD patients.
Methods: This is a narrative review of existing literature. Information was synthesized from academic papers, focusing on CKD pathophysiology and the role, mechanisms, and clinical evidence for SGLT2 inhibitors in providing renal protection
Results: SGLT2 inhibitors protect the kidneys through multiple pathways. They reduce glomerular hyperfiltration by promoting natriuresis and activating tubuloglomerular feedback. They also exhibit anti-inflammatory, anti-oxidative, and anti-fibrotic effects, partly by downregulating the TGF-β pathway. These agents induce a metabolic shift towards ketogenesis, improving mitochondrial energy efficiency. Additional benefits include stimulating erythropoietin (EPO) production to improve tissue oxygenation, modulating autophagy, inhibiting the sympathetic nervous system, improving endothelial function, and reducing serum uric acid. Landmark trials like DAPA-CKD, EMPA-KIDNEY, and CREDENCE have consistently shown that SGLT2 inhibitors significantly reduce GFR decline and progression to end-stage renal disease..
Conclusions: SGLT2 inhibitors represent a fundamental advance in CKD management. Their multifaceted mechanisms offer robust renoprotection beyond glycemic control, supporting their use as a foundational therapy to slow disease progression and lower cardiovascular risk.

Keywords: Chronic Kidney Disease; CKD progression; renoprotection; glomerular hyperfiltration; SGLT2 inhibitors.

INTRODUCTION

Chronic Kidney Disease (CKD) is a progressive medical condition defined by a decline in kidney function lasting more than three months [1]. This condition poses a significant global health challenge, carrying a high risk of severe complications, including end-stage renal disease (ESRD), which requires renal replacement therapies such as dialysis or transplantation [2]. The progression of CKD is often accelerated by underlying factors like hypertension and diabetes [3]. A rapid decline in the glomerular filtration rate (GFR), often accompanied by increased proteinuria, is a key indicator of advancing glomerular damage and cardiovascular risk [4].

Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors, a class of medication originally developed for the management of type 2 diabetes, have emerged as a cornerstone in modern CKD therapy [5]. Their primary mechanism of action involves the inhibition of glucose reabsorption in the proximal renal tubules, which induces a natriuretic effect and reduces intraglomerular pressure, contributing to renal protection [6]. Consequently, the clinical use of SGLT2 inhibitors has expanded to include patients with CKD, with or without diabetes, and is now recommended by major clinical guidelines [7].

Several large-scale clinical trials have validated their role, with studies such as the DAPA-CKD trial showing that dapagliflozin significantly reduced the risk of worsening renal outcomes, even in patients without diabetes [8]. Similarly, the CREDENCE trial confirmed that canagliflozin decreases the risk of both renal events and cardiovascular death in the CKD population [9]. While the clinical benefits are clear, potential side effects like genitourinary infections and a rare risk of ketoacidosis require careful patient monitoring [10]. This review aims to synthesize the current evidence regarding the mechanisms of action and the clinical impact of SGLT2 inhibitors in slowing the progression of chronic kidney disease.

METHODS

This narrative review was conducted to provide a comprehensive overview of the impact of SGLT2 inhibitors on the progression of Chronic Kidney Disease (CKD). The methods section details the approach used for gathering and synthesizing information for this article.

- Sources of information: A literature search was performed utilizing major electronic databases commonly included for medical topics, such as MEDLINE/PubMed and the Cochrane Database of Systematic Reviews. Additionally, the reference lists of retrieved articles were reviewed to identify further relevant publications.
- Search terms and delimiting: The search strategy involved using key terms related to the topic, including "SGLT2 inhibitors," "Chronic Kidney Disease," "CKD progression," and "renoprotection". These terms were used individually and in combination to ensure a thorough search of the available literature.
- Selection criteria employed: Articles were included if they provided detailed information on the mechanisms of action, clinical efficacy, and safety of SGLT2 inhibitors in the context of CKD. The review prioritized landmark clinical trials, systematic reviews, mechanistic studies, and published clinical practice guidelines. Articles were excluded if they were not published in English or did not directly address the impact of SGLT2 inhibitors on renal outcomes. The criteria were designed to be comprehensive without being overly limiting. The selected literature was then critically reviewed and synthesized to present a cohesive and clear flow of ideas.

RESULTS

The literature review reveals that the renoprotective effects of SGLT2 inhibitors are not due to a single mechanism but rather a complex interplay of hemodynamic, metabolic, and anti-inflammatory pathways. These mechanisms work together to slow the progression of chronic kidney disease.

Reduction of Glomerular Hyperfiltration

One of the most significant mechanisms of renal protection is the correction of glomerular hyperfiltration, a primary driver of kidney damage, particularly in diabetic kidney disease. By inhibiting the SGLT2 transporter, these drugs block the reabsorption of sodium and glucose in the proximal tubule. This action increases the delivery of sodium to the macula densa, which in turn activates tubuloglomerular feedback (TGF). The activation of TGF leads to the vasoconstriction of the afferent (incoming) arteriole, which lowers the pathologically high pressure within the glomerulus. This reduction in intraglomerular pressure alleviates the physical strain and filtration burden on the glomeruli, thereby preserving long-term kidney function.

Metabolic Shift and Improved Mitochondrial Energy Supply

SGLT2 inhibitors induce a unique metabolic shift that enhances the energy efficiency of renal cells. By promoting glucosuria, they trigger a systemic change from glucose metabolism to the β-oxidation of fatty acids, which increases the production of ketone bodies like β-hydroxybutyrate. Ketones serve as a more efficient energy source for the kidney's tubular cells, generating more ATP for every unit of oxygen consumed. This improved metabolic efficiency reduces the oxygen demand of the kidneys, alleviates cellular stress, and enhances overall mitochondrial function, protecting the cells from hypoxic injury.

Increased EPO Production and Tissue Oxygenation

The metabolic benefits of SGLT2 inhibitors are linked to improved tissue oxygenation. By reducing the metabolic workload required for glucose reabsorption, these drugs decrease the oxygen consumption of tubular cells, which helps to alleviate the chronic micro-hypoxia often found in the CKD kidney. This improved oxygen environment can enhance the production of erythropoietin (EPO), the hormone responsible for red blood cell production. Clinical studies consistently show that SGLT2 inhibitors lead to a modest increase in hematocrit, which improves the oxygen-carrying capacity of the blood and further protects the kidneys from hypoxia-related inflammation and fibrosis.

Anti-inflammatory, Anti-oxidative, and Anti-fibrotic Effects

Chronic inflammation, oxidative stress, and fibrosis are key pathways leading to irreversible kidney scarring. In CKD, particularly with diabetes, hyperglycemia leads to the formation of advanced glycation end products (AGEs), which trigger inflammatory cascades and the production of reactive oxygen species. This environment activates pro-fibrotic factors, most notably Transforming Growth Factor-β (TGF-β), driving glomerulosclerosis and interstitial fibrosis. SGLT2 inhibitors have been shown to directly counter these processes by suppressing the expression of pro-inflammatory cytokines (like IL-6) and fibrotic drivers.

Inhibition of the Sympathetic Nervous System

Chronic overactivation of the sympathetic nervous system is strongly linked to the progression of CKD, as it promotes glomerulosclerosis, protein loss, and renal fibrosis. SGLT2 inhibitors appear to dampen this harmful activity. They can reduce afferent renal nerve activity, which in turn inhibits systemic sympathetic activation. This effect contributes to lower blood pressure, reduced sodium retention, and a decrease in renal inflammation and fibrosis

Modulation of Autophagy

SGLT2 inhibitors also influence cellular repair mechanisms. They have been shown to modulate key signaling pathways involved in autophagy—the process by which cells clear damaged components and recycle them. By activating pathways such as AMPK and SIRT1, these drugs enhance this cellular "housekeeping," which helps to reduce inflammation, improve cellular homeostasis, and ultimately contributes to renal protection.

Reduction of Uric Acid

Chronic hyperuricemia (elevated uric acid) has been identified as an independent risk factor for the development and progression of CKD. SGLT2 inhibitors promote the urinary excretion of uric acid. This is thought to occur because glucose and urate compete for reabsorption in the renal tubules via transporters like GLUT9. By increasing glucose in the tubular fluid, SGLT2 inhibitors effectively reduce the reabsorption of uric acid, leading to lower serum levels and mitigating another potential source of kidney damage.

DISCUSSION

The emergence of Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors represents arguably the most significant therapeutic advancement in nephrology in the last two decades, fundamentally altering the standard of care for patients with Chronic Kidney Disease (CKD) [11]. The robust and consistent findings from landmark clinical trials—including DAPA-CKD, CREDENCE, and EMPA-KIDNEY—have firmly established their role in slowing the progression of kidney disease and reducing cardiovascular risk across an impressively broad spectrum of patients, including those with and without type 2 diabetes [8, 9, 12]. This has precipitated a critical paradigm shift in management, moving away from a historically reactive, risk-factor-focused approach (primarily targeting hyperglycemia and hypertension) to a proactive strategy centered on direct organ preservation through multiple, synergistic mechanisms [7, 13]. The strength of this evidence now positions SGLT2 inhibitors as a foundational, pillar therapy for most patients with CKD, recommended by major international guidelines to be used in conjunction with renin-angiotensin-aldosterone system (RAAS) inhibitors to achieve comprehensive cardiorenal protection [7]. This evolution in clinical practice is not merely an incremental improvement but a transformative change, offering tangible hope for altering the natural history of a disease that was once considered relentlessly progressive.

The profound clinical success of this drug class is underpinned by its unique and multifaceted mechanisms of action, which extend far beyond their initial purpose of glycemic control [3, 5, 6]. The initial hypothesis centered on their favorable hemodynamic effects—specifically, the reduction of glomerular hyperfiltration through the restoration of tubuloglomerular feedback [5, 6]. By inducing natriuresis and constricting the afferent arteriole, these agents effectively "de-pressurize" the glomerulus, mitigating the physical strain that drives glomerulosclerosis. However, it is now abundantly clear that this hemodynamic effect, while crucial, is just one component of a much larger, integrated protective framework. The true power of SGLT2 inhibitors appears to lie in the synergy of their diverse effects. A pivotal aspect is the metabolic reprogramming they induce. By forcing a state of mild, persistent glycosuria, they trigger a systemic shift from glucose utilization to fat oxidation, increasing the production of ketone bodies [14]. These ketones, particularly β-hydroxybutyrate, serve as a more energy-efficient "superfuel" for both the kidneys and the heart, generating more ATP per unit of oxygen consumed [14]. This improvement in cellular bioenergetics, often termed the "thrifty substrate" hypothesis, is critical for the highly metabolic renal tubular cells, reducing their oxygen demand and protecting them from the hypoxic and metabolic stress that characterizes the CKD microenvironment.

This metabolic benefit is intimately linked with their potent anti-inflammatory, anti-oxidative, and anti-fibrotic properties [3]. The reduction in intracellular glucose and the alleviation of metabolic stress help to downregulate key pathways of injury. SGLT2 inhibitors have been shown to suppress the production of advanced glycation end products (AGEs) and inhibit the downstream inflammatory cascade mediated by the AGE-RAGE axis [3]. Furthermore, they directly modulate pro-fibrotic signaling pathways, most notably by reducing the expression of Transforming Growth Factor-β (TGF-β), a master regulator of fibrosis that drives the excessive deposition of extracellular matrix and leads to irreversible kidney scarring. This combination of hemodynamic and metabolic benefits, coupled with direct anti-inflammatory and anti-fibrotic actions, creates a virtuous cycle of organ protection. The ability of these agents to also improve renal oxygenation—by reducing the metabolic workload of the tubules and subsequently enhancing erythropoietin (EPO) production—further contributes to their protective effects [14]. It is this comprehensive suite of mechanisms, working in concert, that explains their consistent efficacy across CKD of varying etiologies (including non-diabetic causes like hypertensive and ischemic nephropathy) and clarifies why their renoprotective benefits are largely independent of their glucose-lowering effect.

From a clinical implementation standpoint, the widespread adoption of SGLT2 inhibitors requires a nuanced understanding of their safety profile and practical application. The most frequently encountered side effects are genital mycotic infections, a direct consequence of glycosuria, which are typically mild to moderate and can be managed with standard antifungal treatments and patient education on hygiene [10, 15]. The osmotic diuretic effect can increase the risk of volume depletion and hypotension, particularly in elderly or frail patients and those on concurrent loop diuretic therapy. This necessitates careful clinical judgment, often involving a pre-emptive reduction in diuretic dosage upon initiation of the SGLT2 inhibitor, alongside diligent monitoring of volume status and renal function [10]. Although the absolute risk of euglycemic diabetic ketoacidosis (DKA) is low, it remains a serious potential complication. It is imperative that clinicians educate patients on the "sick day rules"—the importance of temporarily discontinuing the medication during periods of acute illness, prolonged fasting, or major surgery—to mitigate this risk. While initial concerns existed regarding their use in patients with lower GFR, data from large trials have been reassuring, demonstrating both safety and efficacy in patients with GFRs as low as 20-25 mL/min/1.73 m², thus expanding the population of patients who stand to benefit [4, 12].

Looking forward, while the current evidence is compelling, several important questions remain. The long-term efficacy and safety of SGLT2 inhibitors in specific CKD populations, such as those with immunologically-mediated glomerulonephritis, polycystic kidney disease, or in kidney transplant recipients, require further dedicated investigation. The potential for combination therapy—for instance, pairing SGLT2 inhibitors with newer agents like non-steroidal mineralocorticoid receptor antagonists (e.g., finerenone)—is a promising area of research that could offer even greater cardiorenal protection. Furthermore, exploring the full spectrum of their systemic benefits, including effects on vascular stiffness, cardiac remodeling, and even cognitive function, will continue to refine our understanding of this remarkable class of drugs. In conclusion, SGLT2 inhibitors have not just added a new tool to the nephrologist's armamentarium; they have fundamentally reshaped our approach to CKD, shifting the focus from managing complications to preserving organ function and improving the long-term health and survival of our patients.

CONCLUSIONS

SGLT2 inhibitors have fundamentally changed the management of Chronic Kidney Disease (CKD). Their multifaceted mechanisms of action, which extend well beyond glycemic control, offer robust renoprotection. The compelling evidence from landmark clinical trials supports their use as a foundational therapy in patients with CKD to slow disease progression and reduce associated cardiovascular risks. Through a powerful combination of hemodynamic, metabolic, and anti-inflammatory effects, these agents significantly slow the decline in kidney function, reduce the risk of progression to end-stage renal disease, and decrease cardiovascular mortality. Consequently, SGLT2 inhibitors have become a cornerstone in the therapeutic strategy for a wide range of patients with CKD, offering new hope for preserving kidney health and improving long-term outcomes.

Author Contributions

Conceptualization, M.I.P. and A.S.; methodology, A.S.; investigation, M.I.P.; writing—original draft preparation, M.I.P.; writing—review and editing, M.I.P. and A.S.; supervision, A.S.; project administration, A.S. All authors have read and agreed to the published version of the manuscript

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Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article as it is a narrative review of existing literature. All data discussed are sourced from previously published studies, which are cited in the reference section.

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Conflicts of Interest

The authors declare no conflict of interest

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