

Renoprotective Effect of SGLT 2 Inhibitors Across Diabetic and Non-Diabetic Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a major health problem that affects individuals with and without diabetes and is associated with progressive loss of kidney function and increased cardiovascular risk. Sodium-glucose cotransporter 2 (SGLT2) inhibitors were initially developed as glucose-lowering agents but have demonstrated substantial renoprotective effects beyond glycemic control. This literature review aimed to evaluate the renoprotective effects of SGLT2 inhibitors in diabetic and non-diabetic CKD, with particular emphasis on their mechanisms of action, effects on renal outcomes, and clinical implications. A narrative literature review was conducted using publications identified through PubMed, ScienceDirect, and Google Scholar. English-language publications published between 2016 and 2026 were considered, with randomized controlled trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines prioritized. The reviewed evidence indicates that SGLT2 inhibitors protect kidney function through restoration of tubuloglomerular feedback, reduction of intraglomerular pressure and hyperfiltration, increased natriuresis, and modulation of inflammatory, oxidative, and fibrotic pathways. Major clinical trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, demonstrated reductions in albuminuria, slower decline in eGFR, and lower risk of kidney disease progression. Importantly, renal benefits were also observed in patients without diabetes, indicating that the effects of SGLT2 inhibitors are not dependent on glucose lowering. Overall, SGLT2 inhibitors represent an important therapeutic option for renoprotection across different CKD populations, although treatment should be individualized according to kidney function, underlying disease, and potential adverse effects.

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1. INTRODUCTION

Chronic kidney disease (CKD) represents a substantial global health challenge and is associated with persistent impairment of renal structure or function. As the disease progresses, patients may develop kidney failure and face an elevated risk of cardiovascular morbidity and mortality [1]. The increasing prevalence and clinical consequences of CKD highlight the importance of interventions capable of maintaining renal function and slowing its progression [2]. Diabetes mellitus is an important cause of CKD, with prolonged metabolic abnormalities contributing to glomerular hyperfiltration, increased intraglomerular pressure, inflammatory processes, and subsequent renal damage. Nevertheless, CKD is not limited to patients with diabetes and may arise from other conditions, including hypertension, glomerular disorders, and tubulointerstitial diseases

[1]. Consequently, therapeutic approaches that provide renal protection across different underlying causes of CKD are of particular clinical interest.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors were originally developed to improve glycemic control in individuals with type 2 diabetes mellitus. Their pharmacological action reduces the reabsorption of glucose and sodium within the proximal tubule, resulting in effects that extend beyond glucose regulation [3]. Several mechanisms have been proposed to explain their protective effects on the kidney, including improvement of tubuloglomerular feedback, attenuation of glomerular hyperfiltration and intraglomerular pressure, and regulation of inflammatory, oxidative, and fibrotic processes [4], [5]. These findings indicate that the renal benefits associated with SGLT2 inhibition may be partly independent of its glucose-lowering action.

Clinical evidence supporting these effects initially emerged from studies involving patients with diabetic kidney disease. In the CREDENCE trial, treatment with canagliflozin was associated with a lower incidence of clinically significant renal and cardiovascular outcomes among patients with type 2 diabetes and albuminuric CKD [6]. The potential application of SGLT2 inhibitors subsequently expanded to patients without diabetes. The DAPA-CKD trial reported that dapagliflozin reduced the likelihood of kidney disease progression or death attributable to renal causes, with benefits observed in participants both with and without type 2 diabetes [7]. Consistent findings were reported in the EMPA-KIDNEY trial, in which empagliflozin reduced the risk of kidney disease progression or cardiovascular death across a diverse CKD population, including patients without diabetes [8].

These findings have shifted the clinical perspective on SGLT2 inhibitors from their original role as glucose-lowering medications toward their broader application in renal and cardiovascular protection. Current recommendations support their use in appropriately selected patients with CKD irrespective of diabetes status [1]. However, diabetic and non-diabetic CKD may differ in their underlying mechanisms and clinical characteristics. Consequently, whether the magnitude and nature of the renal benefits associated with SGLT2 inhibition are comparable between these populations remains clinically relevant. A synthesis of the available evidence may help clarify the mechanisms and clinical significance of these effects across different CKD populations. Therefore, this literature review examines the renoprotective effects of SGLT2 inhibitors in patients with diabetic and non-diabetic CKD, focusing on their proposed mechanisms, kidney-related outcomes, and similarities and differences in therapeutic effects between the two populations.

2. METHODS

This article was developed as a literature review focusing on the renoprotective effects of SGLT2 inhibitors in patients with chronic kidney disease (CKD), irrespective of diabetes status. Relevant literature was searched through PubMed, ScienceDirect, and Google Scholar. The search incorporated terms related to SGLT2 inhibition and CKD, including “SGLT2 inhibitor,” “chronic kidney disease,” “diabetic kidney disease,” “non-diabetic chronic kidney disease,” “renoprotection,” and “renal outcomes.” Boolean operators were applied to combine the search terms and improve the identification of publications relevant to the scope of the review. Publications issued between 2016 and 2026 were preferentially considered to reflect contemporary evidence on SGLT2 inhibitor use in CKD.

A total of 102 publications were identified through the database searches. After removal of 27 duplicate records, 75 unique publications remained for screening. The selection of references was based primarily on their relevance to the objectives of the

review. English-language publications examining SGLT2 inhibitor therapy in patients with CKD and reporting information related to kidney function or renal outcomes were considered eligible. Randomized controlled trials, observational studies, systematic reviews, meta-analyses, and relevant clinical guidelines were prioritized as the main sources of evidence. Case reports, editorials, letters to the editor, duplicate publications, and studies that did not provide relevant renal outcomes were excluded.

The 75 unique publications were initially assessed based on their titles and abstracts to determine their relevance to the review topic. Publications considered potentially eligible were subsequently examined in full text. Information extracted from the selected literature included study population, SGLT2 inhibitor used, diabetes status, baseline kidney function, and treatment-related renal outcomes. Particular emphasis was placed on changes in estimated glomerular filtration rate (eGFR), albuminuria, decline in kidney function, progression to kidney failure, and composite renal endpoints. Following the screening and eligibility assessment process, 18 studies that met the predefined inclusion criteria were included in the final narrative synthesis.

The selected evidence was subsequently organized and interpreted using a descriptive thematic approach. Findings concerning the mechanisms of SGLT2-mediated kidney protection and clinical outcomes were examined separately in diabetic and non-diabetic CKD populations. Comparisons were then made to identify common patterns of benefit as well as potential differences between the two populations. Because this review followed a narrative rather than quantitative synthesis approach, no statistical pooling of treatment effects or independent meta-analysis was performed.

3. RESULTS AND DISCUSSION

3.1 Mechanisms of Renoprotection by SGLT2 Inhibitors

The kidney-protective effects of SGLT2 inhibitors are largely associated with their influence on proximal tubular transport and glomerular hemodynamics. Under physiological conditions, SGLT2 is responsible for reabsorbing a substantial proportion of filtered glucose together with sodium in the proximal tubule [9]. Pharmacological inhibition of this transporter increases urinary glucose and sodium excretion, thereby enhancing sodium delivery to the macula densa. This alteration promotes the restoration of tubuloglomerular feedback (TGF), which subsequently modifies afferent arteriolar tone and contributes to a reduction in intraglomerular pressure [10].

The restoration of TGF is particularly relevant to the control of glomerular hyperfiltration. In diabetes, increased proximal tubular reabsorption of glucose and sodium reduces sodium delivery to the macula densa, resulting in an attenuated TGF response. The consequent persistence of afferent arteriolar dilation contributes to elevated intraglomerular pressure and hyperfiltration, processes that may accelerate renal injury. By increasing distal sodium delivery, SGLT2 inhibition helps re-establish this feedback mechanism and reduces glomerular hyperfiltration. An early decline in eGFR may consequently occur after treatment initiation, reflecting an acute hemodynamic response rather than structural renal damage. This initial change is generally reversible and is followed by a slower decline in kidney function over the longer term [11].

Renal protection associated with SGLT2 inhibition may also involve mechanisms beyond changes in glomerular hemodynamics. Chronic tubular stress, increased oxygen demand, oxidative imbalance, and activation of inflammatory pathways can contribute to progressive renal injury and fibrosis. Experimental and translational evidence suggests that SGLT2 inhibition may modulate inflammatory signaling and pathways involved in inflammasome activation, while also attenuating processes associated with renal fibrotic

remodeling [12], [13]. Although the evidence for these effects is derived predominantly from experimental and mechanistic studies, they provide additional biological explanations for the renal benefits observed with SGLT2 inhibitors.

Taken together, the renoprotective action of SGLT2 inhibitors appears to arise from multiple complementary processes rather than from a single mechanism. Hemodynamic changes involving TGF, intraglomerular pressure, and hyperfiltration occur relatively early, whereas effects on tubular workload, inflammation, oxidative stress, and fibrosis may contribute to sustained preservation of renal structure and function [9], [12]. Importantly, these mechanisms are not entirely dependent on glucose lowering, which may help explain why SGLT2 inhibitors can provide renal protection in patients with CKD even in the absence of diabetes.

3.2 Renoprotective Effects in Diabetic CKD

Evidence from major clinical trials has established the renoprotective effects of SGLT2 inhibitors in patients with diabetic CKD. The CREDENCE trial demonstrated that canagliflozin reduced the risk of a composite renal outcome consisting of end-stage kidney disease, doubling of serum creatinine, or renal or cardiovascular death compared with placebo. The risk of end-stage kidney disease alone was also lower among patients receiving canagliflozin, providing direct evidence of its ability to delay clinically important kidney outcomes in diabetic CKD [6].

In addition to reducing major renal outcomes, SGLT2 inhibition has been associated with improvements in albuminuria and preservation of kidney function. In CREDENCE, canagliflozin reduced urinary albumin-to-creatinine ratio by approximately 31% during follow-up. The trial also demonstrated a slower rate of eGFR decline after the initial hemodynamic reduction in eGFR, indicating that the early change in kidney function was followed by a more favorable long-term trajectory [6].

Evidence from DAPA-CKD further supports the renal benefits of dapagliflozin in CKD populations that included a substantial proportion of patients with type 2 diabetes. The treatment reduced the risk of the primary composite outcome, which included a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. Importantly, the beneficial effect was observed in participants with type 2 diabetes as well as those without diabetes, suggesting that the renal effects of dapagliflozin are not restricted to diabetic kidney disease [14].

EMPA-KIDNEY provided additional evidence for the renal benefits of empagliflozin in patients with CKD, including those with diabetes. The trial showed a lower risk of kidney disease progression or cardiovascular death with empagliflozin compared with placebo, with consistent effects among participants with and without diabetes. Together, CREDENCE, DAPA-CKD, and EMPA-KIDNEY indicate that SGLT2 inhibitors can reduce albuminuria, slow the decline in kidney function, and lower the risk of progression toward kidney failure in patients with diabetic CKD [8].

3.3 Renoprotective Effects in Non-Diabetic CKD

The renal benefits of SGLT2 inhibitors extend beyond patients with diabetes. A prespecified analysis of DAPA-CKD demonstrated that the effect of dapagliflozin on major kidney and cardiovascular outcomes was consistent between participants with type 2 diabetes and those without diabetes. Among participants without diabetes, dapagliflozin was associated with a lower risk of the primary composite outcome, supporting its use as a potential renoprotective therapy independent of diabetes status [14].

The EMPA-KIDNEY trial provided further evidence in a broad CKD population. Empagliflozin reduced the risk of kidney disease progression or cardiovascular death compared with placebo, and the treatment effect was consistent among participants with and without diabetes as well as across different levels of baseline eGFR [8]. These findings indicate that the kidney-protective effects of SGLT2 inhibition are not dependent on the presence of hyperglycemia and may therefore be relevant to patients with CKD who do not have diabetes.

The potential application of SGLT2 inhibitors across different non-diabetic CKD etiologies is also supported by secondary analyses of EMPA-KIDNEY. Participants included individuals with diabetic kidney disease, glomerular diseases, hypertensive or renovascular disease, and other or unknown causes of CKD. The relative effect of empagliflozin on kidney disease progression did not significantly differ according to the primary kidney disease, while the rate of chronic eGFR decline was reduced across these disease categories [17].

Overall, evidence from DAPA-CKD and EMPA-KIDNEY indicates that SGLT2 inhibitors can provide meaningful renal protection in selected patients with CKD without diabetes. Their effects include slowing kidney function decline and reducing the risk of progression to advanced kidney disease. The consistency of treatment effects across diabetes status and several underlying kidney diseases further supports the concept that SGLT2-mediated renal protection involves mechanisms beyond glucose lowering [8], [17].

3.4 Comparison and Clinical Implications

Evidence from major clinical trials suggests that the renoprotective effects of SGLT2 inhibitors are broadly comparable in patients with and without diabetes. DAPA-CKD demonstrated a consistent reduction in major kidney and cardiovascular outcomes across diabetes status, while EMPA-KIDNEY similarly reported consistent treatment effects among participants with and without diabetes [8], [14]. These findings indicate that the therapeutic role of SGLT2 inhibitors extends beyond the management of diabetic kidney disease.

The persistence of renal benefits in individuals without diabetes suggests that these effects are not primarily dependent on glycemic control. Instead, mechanisms involving tubuloglomerular feedback, intraglomerular hemodynamics, natriuresis, and tubular metabolic changes are likely to contribute to kidney protection. This distinction is clinically important because it supports the use of SGLT2 inhibitors for renal protection even when their glucose-lowering effect is absent or limited [11], [14].

These findings have expanded the role of SGLT2 inhibitors from glucose-lowering agents to an important component of CKD management. Current KDIGO recommendations support SGLT2 inhibitor therapy in appropriate patients with CKD, including adults with an eGFR of at least 20 mL/min/1.73 m² and significant albuminuria, as well as patients with heart failure irrespective of albuminuria [1]. The available evidence also supports their use across a range of CKD etiologies, although the strength and applicability of evidence may differ according to the underlying kidney disease and patient characteristics.

SGLT2 inhibitors are generally well tolerated, but treatment should be accompanied by appropriate clinical monitoring. A reversible reduction in eGFR may occur shortly after initiation and is generally considered a hemodynamic effect rather than an indication for treatment discontinuation. Volume depletion should also be considered, particularly in patients with concomitant diuretic therapy or an increased risk of hypovolemia. In patients with diabetes, the risk of diabetic ketoacidosis, including euglycemic diabetic ketoacidosis,

should be recognized, and temporary withholding of therapy may be appropriate during prolonged fasting, surgery, or critical illness [1], [6].

4. CONCLUSION

Current evidence indicates that SGLT2 inhibitors provide kidney-protective effects across a broad range of patients with chronic kidney disease, including those with and without diabetes. These effects are associated with several complementary mechanisms, particularly improved tubuloglomerular feedback, attenuation of glomerular hyperfiltration and intraglomerular pressure, and modulation of inflammatory and fibrotic processes. Findings from major clinical trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, further demonstrate their ability to reduce albuminuria, preserve kidney function, and delay progression toward kidney failure. The persistence of these benefits among individuals without diabetes suggests that the renal effects of SGLT2 inhibitors extend beyond their glucose-lowering action. Thus, SGLT2 inhibitors represent an important therapeutic option for CKD management across different diabetes statuses, with treatment requiring appropriate consideration of patient characteristics and potential adverse effects.

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