



Sodium-glucose cotransporter 2 inhibitors; revolutionizing diabetic kidney disease management

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Abstract

Diabetic kidney disease (DKD), a leading cause of kidney failure, is driven by hyperglycemia and inflammation. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, initially for type 2 diabetes, transform DKD treatment by reducing glucose reabsorption, easing glomerular pressure, and shortening inflammation. These drugs are safe, with minor risks. Combining with GLP-1 agonists or mineralocorticoid antagonists may boost benefits. In addition, SGLT2 inhibitors slow DKD progression, enhancing patient outcomes. Future studies should refine combination therapies and personalized care.

Keywords: Diabetic Nephropathies, Sodium-Glucose Transporter 2 Inhibitors, Renal Insufficiency

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Introduction

Diabetic kidney disease (DKD), commonly referred to as diabetic nephropathy, is among the most serious issues arising from diabetes mellitus, especially type 2 diabetes (T2DM) (1). It features ongoing kidney damage, shown through protein in the urine, reduced glomerular filtration rate (GFR), and ultimate advancement to end-stage renal disease (ESRD) (2). Worldwide, DKD stands as the top reason for chronic kidney disease (CKD) and ESRD, creating a heavy load on health services and affecting individuals' well-being. The development of DKD involves various factors, such as elevated blood sugar causing excessive filtration in the glomeruli, free radical damage, inflammation, and tissue scarring, all leading to changes in kidney structure and function (3).

In the past, DKD treatment has centered on maintaining blood sugar levels, controlling hypertension using renin-angiotensin-aldosterone system (RAAS) blockers like angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and adopting healthy habits (4). While these strategies have slowed progression, they have not halted it entirely, leaving a critical unmet need for therapies that offer robust renoprotection (5). The advent of sodium-glucose cotransporter 2 (SGLT2) inhibitors marks a paradigm shift in this landscape (6). Initially developed as antidiabetic agents to promote glycosuria and improve glycemic control, SGLT2 inhibitors have demonstrated profound benefits beyond glucose lowering,

particularly in cardiovascular and renal outcomes (7).

SGLT2 inhibitors, such as canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, mainly function by blocking the SGLT2 protein in the kidney's proximal tubule, which handles about 90% of glucose reuptake from filtered fluid (8). This inhibition leads to increased urinary glucose excretion, reducing hyperglycemia in diabetic patients (9). However, the renoprotective effects extend far beyond this, encompassing hemodynamic, metabolic, and anti-inflammatory actions that directly address the core pathologies of DKD (3).

This narrative review aims to explore the evolving role of SGLT2 inhibitors in reshaping the management of DKD. We will delve into their mechanisms of action, synthesize evidence from investigations, evaluate their safety profile in patients with DKD, and discuss future directions, including combination therapies.

Method of Search

This narrative review evaluated SGLT2 inhibitors in DKD management through a literature search in PubMed, Embase, and Cochrane Library (2010–2025). Search terms included “SGLT2 inhibitors,” “diabetic nephropathy,” and “renoprotection.”

Results and Discussion

Globally, the International Diabetes Federation estimates that over 500 million people live with diabetes, a number

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■ Implication for health policy/practice/research/medical education

Sodium-glucose cotransporter 2 (SGLT2) inhibitors should be integrated into clinical practice and health policies to improve outcomes and slow progression in diabetic kidney disease (DKD). Future research and medical education should focus on long-term safety, combination therapies, and equipping clinicians with evidence-based management strategies.

projected to rise to 700 million by 2045, amplifying the DKD epidemic (10). Traditional therapies like RAAS blockade have reduced progression by 20-30%, but residual risk remains high (11). SGLT2 inhibitors address this gap, offering relative risk reductions in renal endpoints (12). Their approval for CKD indications, irrespective of diabetes status in some cases, further broadens their applicability (13).

Mechanism of action of SGLT2 inhibitors in DKD

The kidney-protecting benefits of SGLT2 inhibitors in DKD involve multiple aspects, including blood flow regulation, metabolic shifts, inflammation reduction, and anti-scarring effects. At the core is their inhibition of the SGLT2 transporter in the proximal convoluted tubule (14). In healthy kidneys, SGLT2 reabsorbs sodium and glucose in a coupled manner, but in diabetes, hyperglycemia upregulates SGLT2 expression, leading to excessive reabsorption. This exacerbates glomerular hyperfiltration, a hallmark of early DKD, where increased intraglomerular pressure damages podocytes and mesangial cells (15).

By blocking SGLT2, these inhibitors promote natriuresis and glucosuria, reducing proximal sodium reabsorption (16). This condition activates tubuloglomerular feedback, where increased sodium delivery to the macula densa prompts afferent arteriolar vasoconstriction, lowering glomerular pressure and hyperfiltration. Studies in diabetic models show that this mechanism normalizes GFR and reduces albuminuria within weeks of initiation (17).

Beyond hemodynamics, metabolic effects play a crucial role. Glucosuria induces a mild caloric deficit, promoting weight loss and improving insulin sensitivity (18). In DKD, this mitigates glucotoxicity, reducing advanced glycation end-products (AGEs) that contribute to renal fibrosis (3). Additionally, SGLT2 inhibitors shift energy metabolism toward ketone utilization, which is more efficient and less oxygen-consuming, protecting hypoxic renal tissues (19). In proximal tubular cells, reduced glucose uptake decreases ATP demand, alleviating oxidative stress from mitochondrial overload (20).

Anti-inflammatory actions are equally pivotal. DKD involves chronic low-grade inflammation, with elevated cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). SGLT2 inhibitors suppress nuclear factor-kappa B (NF- κ B) signaling, reducing IL-

6, monocyte chemoattractant protein-1 (MCP-1), and other mediators. Also, they induce decreased macrophage infiltration and inflammasome activation in the kidney (21). In human biopsies from DKD patients, empagliflozin treatment correlated with lower inflammatory markers (22).

Fibrosis, a late-stage feature of DKD, is also targeted. Transforming growth factor-beta (TGF- β) drives extracellular matrix accumulation, leading to glomerulosclerosis and tubulointerstitial fibrosis. SGLT2 inhibition downregulates TGF- β and fibronectin expression, as shown in streptozotocin-induced diabetic rats. This antifibrotic effect may involve AMP-activated protein kinase (AMPK) activation, which inhibits profibrotic pathways (23).

Furthermore, SGLT2 inhibitors influence renal oxygen handling. In diabetes, increased proximal reabsorption heightens cortical oxygen consumption, creating medullary hypoxia. By shifting reabsorption distally, these drugs improve oxygenation, reducing hypoxia-inducible factor-1 α (HIF-1 α) expression and erythropoietin production, which may explain observed hematocrit increases (24).

In patients with reduced eGFR, initial concerns about acute kidney injury (AKI) due to volume depletion have been alleviated. Instead, the early eGFR dip is reversible and protective, akin to RAAS inhibitors, reflecting reduced hyperfiltration rather than harm. Long-term, this preserves renal function (25).

Cardiorenal interactions are noteworthy. SGLT2 inhibitors reduce cardiac preload via natriuresis, alleviating congestion in heart failure, which often coexists with DKD. This symbiotic protection enhances overall outcomes (3).

Emerging evidence suggests immunomodulatory effects. A narrative review highlights how SGLT2 inhibitors modulate T-cell responses and reduce pro-inflammatory cytokines, potentially benefiting autoimmune aspects of DKD. In summary, the mechanisms converge to halt DKD progression at multiple levels, from early hyperfiltration to late fibrosis, positioning SGLT2 inhibitors as versatile agents (26).

Clinical evidence from key trials

The clinical efficacy of SGLT2 inhibitors in DKD is robustly supported, transitioning from cardiovascular outcome trials (CVOTs) to dedicated renal trials. Early CVOTs like EMPA-REG OUTCOME (empagliflozin), CANVAS (canagliflozin), and DECLARE-TIMI 58 (dapagliflozin) provided initial signals of renoprotection in secondary analyses (e.g., doubling of serum creatinine, ESKD, or renal death) (27).

The pivotal CREDENCE trial (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) was the first dedicated renal outcome study. Enrolling 4,401 patients with T2DM, albuminuria (>300

mg/g), and eGFR 30-90 mL/min/1.73 m², all on RAAS blockade, it compared canagliflozin 100 mg to placebo. The primary composite endpoint (ESKD, doubling of creatinine, or renal/cardiovascular death) was reduced by 30% (HR 0.70; 95% CI 0.59-0.82). Albuminuria decreased by 31%, and eGFR decline slowed by 2.74 mL/min/1.73 m² per year. Benefits were consistent across subgroups, including those with eGFR <45 mL/min/1.73 m² (28).

Expanding on the previous findings, the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) study broadened the scope to include non-diabetic CKD (29). This trial enrolled 4,304 participants, with 67% diagnosed with type 2 diabetes mellitus (T2DM), featuring an estimated glomerular filtration rate (eGFR) between 25-75 mL/min/1.73 m² and albuminuria ranging from 200-5000 mg/g. Treatment with dapagliflozin at a 10 mg dose resulted in a 39% reduction in the primary endpoint—defined as a sustained \geq 50% decline in eGFR, ESKD, or renal/cardiovascular death—yielding a hazard ratio (HR) of 0.61 (95% CI 0.51-0.72). Among the diabetic subgroup, the risk reduction was 36%. Significantly, the positive effects extended to non-diabetic participants, thereby widening the potential applications of the treatment (30,31).

EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin) further expanded the evidence base. With 6,609 patients (31% without diabetes), eGFR 20-45 mL/min/1.73 m² or 45-90 with albuminuria \geq 200 mg/g, empagliflozin 10 mg lowered the primary endpoint (kidney disease progression or cardiovascular death) by 28% (HR 0.72; 95% CI 0.64-0.82). Progression was defined as ESKD, sustained \geq 40% eGFR decline, or renal death. The trial was stopped early for efficacy, highlighting rapid benefits (32).

Real-world studies verify data. Observational cohorts report similar reductions in renal events, with hazard ratios aligning with RCTs. Subgroup analyses indicate benefits in advanced DKD, with eGFR as low as 20 mL/min/1.73 m² (33,34).

Safety profile in patients with DKD

While efficacious, the safety of SGLT2 inhibitors in DKD warrants scrutiny, given renal impairment's potential to alter pharmacokinetics. Overall, their profile is favorable, with low rates of serious adverse events (3,35).

Common side effects include genital mycotic infections, occurring due to glucosuria, more frequent in women but rarely severe (36). Urinary tract infections are mildly elevated but not significantly in DKD cohorts (37).

Volume depletion-related events, like hypotension or dehydration, affect particularly in elderly or diuretic users. However, these are manageable with dose adjustments (38).

Concerns about AKI have been dispelled and reduced AKI risk attributed to hemodynamic protection has been noted. The initial eGFR dip is transient. Euglycemic

diabetic ketoacidosis is rare (<0.1%), mainly in T1DM or insulin-deficient states, but vigilance is advised in DKD. Amputation risk, was not consistent across trials (25,39).

Combination therapies in future

Looking ahead, combination therapies hold promise. Pairing SGLT2 inhibitors with GLP-1 receptor agonists (GLP-1RAs) or non-steroidal mineralocorticoid antagonists (nsMRAs) like finerenone could amplify benefits. The FIDELIO-DKD trial showed finerenone reduces renal progression; combining with empagliflozin further lowers albuminuria (40,41).

GLP-1RAs complement by reducing appetite and cardiovascular risk (42). Triple therapy (SGLT2i + GLP-1RA + nsMRA) may extend event-free survival by years (43). Ongoing trials explore broader indications, including T1DM and pediatric DKD. Precision medicine, targeting genotypes, is emerging (44).

Conclusion

SGLT2 inhibitors have revolutionized DKD management, offering renoprotection through innovative mechanisms and proven clinical benefits. With a solid safety profile and promising combinations, they herald a new era, potentially curbing the DKD epidemic.

Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

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