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Management of Diabetic Nephropathy: Emerging Evidence with a Focus on Oral Antihyperglycemic Agents

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Abstract

Background: Diabetic nephropathy (DN), also termed diabetic kidney disease (DKD), represents one of the most prevalent microvascular complications of diabetes mellitus and remains a major contributor to chronic kidney disease (CKD) and end-stage kidney disease (ESKD) globally. Its progression is driven by sustained hyperglycaemia, oxidative stress, inflammatory pathways, and activation of the renin–angiotensin–aldosterone system, leading to progressive renal damage and increased cardiovascular morbidity and mortality.

Objective: To assess the efficacy and safety of oral anti-hyperglycaemic agents in the management of diabetic nephropathy, with a particular focus on their reno-protective properties and suitability in patients with CKD.

Methods: A comprehensive literature review was undertaken using electronic databases, including PubMed and the Cochrane Library. To ensure broad coverage of the available evidence, additional searches were performed using Google Scholar and other internet-based sources Selection criteria were defined. Studies evaluating the impact of oral antihyperglycemic therapies on renal outcomes, glycaemic control, and safety profiles in patients with diabetic nephropathy were identified and critically appraised.

Results: A total of 1,246 records were identified through database searching, with 978 unique records remaining after removal of duplicates. After title and abstract screening, 132 articles were selected for full-text review based on predefined eligibility criteria. Of these, 114 studies were excluded due to irrelevant outcomes, non-human data, duplicate findings, review-only designs, or insufficient renal outcome reporting. Finally, 18 studies were included in the qualitative synthesis. These comprised randomized controlled trials, post hoc analyses, and observational studies evaluating oral antihyperglycemic agents in diabetic nephropathy. Overall, SGLT2 inhibitors showed consistent renal protective effects, while DPP-4 inhibitors demonstrated less consistent and modest benefits.

Conclusion: Current evidence supports the role of SGLT2 inhibitors and DPP-4 inhibitors as valuable therapeutic options in diabetic nephropathy. In addition to glycaemic control, these agents provide significant reno-protective and cardioprotective effects, underscoring their importance in modern management strategies for diabetic kidney disease.

Keywords: Diabetic nephropathy; Diabetic kidney disease; SGLT2 inhibitors; DPP-4 inhibitors; chronic kidney disease.

Introduction

Diabetic nephropathy (DN), also referred to as diabetic kidney disease (DKD), represents one of the most prevalent and clinically significant microvascular complications of diabetes mellitus [1]. It is a major cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) globally, playing a major role in long-term morbidity, mortality, and healthcare burden [2]. The condition develops primarily because of chronic exposure to hyperglycaemia, and its progression is frequently accelerated by the coexistence of additional metabolic and cardiovascular risk factors, including hypertension, obesity, dyslipidaemia, and tobacco use [3]. These interacting agents collectively contribute to progressive renal injury and functional decline. Clinically, diabetic nephropathy is characterized by a predictable but progressive course [3]. In its early stages, it is commonly identified by microalbuminuria, reflecting initial glomerular injury and increased permeability of the filtration barrier [3]. As the disease advances, patients may develop macroalbuminuria, accompanied by a continuous decline in glomerular filtration rate (GFR), progressive nephron loss, and ultimately irreversible renal failure [4]. In addition to its direct renal consequences, diabetic nephropathy is strongly associated with an increased risk of cardiovascular morbidity and mortality, thereby representing a double burden harming both renal and systemic vascular health [5].

The global prevalence of diabetic nephropathy is increasing in parallel with the rising incidence of diabetes mellitus [6]. Epidemiological evidence suggests that approximately 30–40% of individuals with type 1 diabetes and 25–40% of those with type 2 diabetes will develop some degree of nephropathy during their lifetime [2,7]. This burden is especially marked in regions undergoing rapid epidemiological transitions and increasing diabetes prevalence, including parts of the Middle East and other developing regions. Consequently, diabetic kidney disease is projected to remain a major driver of end-stage renal disease, disability-adjusted life years, and healthcare expenditure worldwide [8]. The pathogenesis of diabetic nephropathy is multifactorial and involves an intricate interaction of metabolic, hemodynamic, and inflammatory mechanisms. Chronic hyperglycaemia

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plays a central role by promoting the formation of advanced glycation end products (AGEs), which accumulate in renal tissues and alter structural and functional integrity [4]. Hyperglycaemia additionally enhances oxidative stress by increasing the production of reactive oxygen species (ROS), leading to endothelial dysfunction, podocyte injury, and activation of pro-inflammatory pathways [9]. In parallel, activation of the renin–angiotensin–aldosterone system (RAAS) contributes to intraglomerular hypertension and exacerbates mechanical stress on glomerular structures [10].

These processes collectively result in characteristic histopathological alterations, including thickening of the glomerular basement membrane, mesangial expansion, podocyte depletion, and progressive accumulation of extracellular matrix proteins [10]. Over time, these changes lead to glomerulosclerosis and tubulointerstitial fibrosis, culminating in irreversible nephron loss and declining renal function [10]. Additional molecular mediators, such as transforming growth factor-beta (TGF-β), inflammatory cytokines, and various growth factors, additionally enhance fibrotic processes and accelerate disease progression [10]. Traditionally, the management of diabetic nephropathy has focused on strict glycaemic control, optimal blood pressure regulation, and inhibition of the RAAS pathway [10]. Intensive glycaemic control is still a fundamental therapeutic strategy, as sustained hyperglycaemia is a key determinant of microvascular complications. Landmark clinical trials have reliably demonstrated that improved glycaemic control reduces both the onset and progression of diabetic nephropathy. Similarly, effective blood pressure management is critical, as systemic hypertension accelerates renal injury and significantly increases cardiovascular risk [11].

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have long been established as cornerstone therapies in the management of diabetic kidney disease [12]. These agents exert reno-protective effects by reducing intraglomerular pressure, decreasing proteinuria, and slowing the decline in renal function [12]. However, despite the widespread use of RAAS blockade, a substantial proportion of patients continue to experience progressive renal deterioration, illustrating the need for additional clinical interventions that target alternative pathogenic pathways [13]. In recent years, the therapeutic landscape for diabetic nephropathy has advanced considerably, with a shift toward interventions that provide direct renal and cardiovascular protection surpassing glucose-lowering alone. Contemporary clinical guidelines currently emphasize individualized, patient-centred treatment strategies that consider comorbid conditions such as CKD, cardiovascular disease, obesity, risk of hypoglycaemia, treatment affordability, and patient preferences [10]. Within this developing framework, sodium–glucose cotransporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors have appeared as important oral antihyperglycemic agents with potential reno-protective properties [10].

DPP-4 inhibitors are widely used for their favourable safety profile, oral administration, and low risk of hypoglycaemia [14]. These agents function by inhibiting the degradation of incretin hormones, therefore enhancing glucose-dependent insulin secretion and suppressing glucagon release [15]. In patients with renal impairment, most DPP-4 inhibitors require dose adjustment, except linagliptin, which is predominantly eliminated via non-renal pathways and does not require dose adjustment in CKD [16]. Clinically, DPP-4 inhibitors produce modest reductions in glycated haemoglobin (HbA1c), generally ranging from 0.5% to 0.8% [17]. Emerging evidence also points to possible reno-protective effects, including reductions in albuminuria and attenuation of inflammatory and fibrotic pathways, although these effects are generally considered secondary to their glycaemic action [18].

In contrast, SGLT2 inhibitors have proved strong and consistent renal and cardiovascular benefits, identifying them as disease-modifying agents in diabetic kidney disease [19]. These agents act by inhibiting glucose and sodium reabsorption in the proximal renal tubule, leading to glycosuria, natriuresis, and restoration of tubule-glomerular feedback. Importantly, their renal-protective effects extend beyond glycaemic control [19]. Multiple large-scale randomized controlled trials have confirmed the efficacy of SGLT2 inhibitors in reducing the progression of CKD and major renal outcomes. The EMPA-REG OUTCOME trial [20] first showed significant reductions in the incidence or worsening of nephropathy with empagliflozin. Subsequently, dedicated renal outcome trials, including CREDENCE [21], DAPA-CKD [22], and EMPA-KIDNEY [23], further established their capacity to reduce the risk of kidney failure, slow the decline in GFR, and improve composite renal endpoints in both diabetic and non-diabetic CKD populations.

The mechanisms underlying these benefits include reductions in intraglomerular pressure, improvements in renal hemodynamic, attenuation of inflammatory and oxidative pathways, and reductions in renal fibrosis [24]. Additionally, SGLT2 inhibitors improve metabolic efficiency and reduce renal workload, thereby contributing to sustained preservation of kidney function [25]. The consistency and magnitude of benefit observed among varied patient populations have led to their incorporation into major international diabetes and nephrology guidelines [10]. Despite these therapeutic advances, the management of diabetic nephropathy is still complex. Progressive renal impairment affects drug pharmacokinetics and increases the risk of adverse effects, including hypoglycaemia, calling for careful dose adjustment and individualized treatment planning. Glycaemic targets must therefore be customized to patient age, comorbid conditions, disease duration, life expectancy, and the degree of renal dysfunction [26]. Early detection through routine screening for albuminuria and periodic assessment of renal function is essential for timely initiation of reno-protective therapy and prevention of disease progression [27].

To summarize, diabetic nephropathy is still a major worldwide health challenge marked by complex pathophysiology and progressive renal decline. While conventional therapeutic approaches such as glycaemic and blood pressure control and RAAS inhibition remain foundational, newer classes of oral hypoglycaemic agents, particularly SGLT2 inhibitors and DPP-4 inhibitors-offer additional renal and cardiovascular benefits. This review intends to evaluate the efficacy and safety of oral hypoglycaemic agents for managing diabetic nephropathy, with a focus on their role in delaying disease progression and improving clinical outcomes.

Methodology

Literature Search Strategy: A comprehensive literature search was carried out using major electronic databases, including PubMed and the Cochrane Library. To ensure broad coverage of the available evidence, additional searches were performed using Google Scholar and other internet-based sources. The search strategy incorporated the following keywords and their combinations: *diabetic nephropathy*, *diabetic kidney disease*, *oral antihyperglycemic agents*, *oral hypoglycaemic agents*, *sodium–glucose cotransporter-2 (SGLT2) inhibitors*, and *dipeptidyl peptidase-4 (DPP-4) inhibitors*.

The review was restricted to studies involving human participants and to articles published in English between January 2015 and June 2026.

Study Selection: Titles and abstracts identified through the search strategy were independently screened by a reviewer to determine their relevance. Full-text articles of potentially eligible studies were subsequently assessed according to predetermined inclusion and exclusion criteria. Studies meeting the eligibility criteria were included in the final review.

Population: The target population comprised adults with type 2 diabetes mellitus and any stage of diabetic nephropathy or diabetic kidney disease.

Inclusion Criteria: Studies were included if they met the following criteria:

- Participants were diagnosed with type 2 diabetes mellitus.
- Participants had evidence of diabetic nephropathy, diabetic kidney disease, or renal impairment attributable to diabetes.
- Studies evaluated the efficacy and/or safety of oral antihyperglycemic agents in the management of diabetic nephropathy.
- Articles were published between January 2015 and June 2020.
- Study designs included randomized controlled trials, systematic reviews, and meta-analyses.

Exclusion Criteria: Studies were excluded if they met any of the following criteria:

- Failure to satisfy the inclusion criteria.
- Duplicate publications.
- Animal or preclinical studies.
- Articles published before January 2015.
- Non-English language publications.

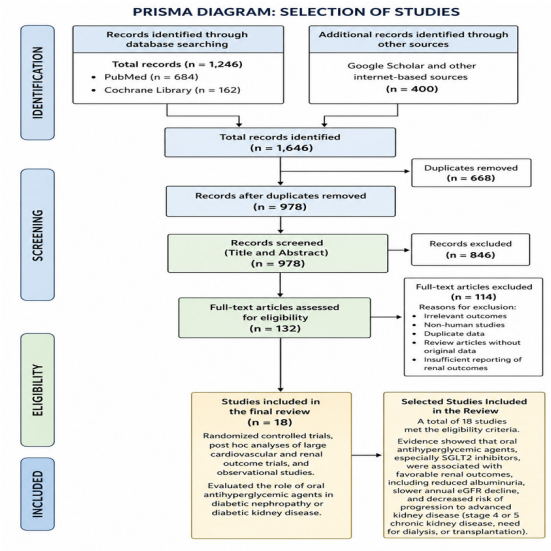
Primary Outcome: The primary outcome was the effectiveness and safety of oral antihyperglycemic agents in patients with diabetic nephropathy, assessed primarily by their ability to prevent the progression of albuminuria and preserve renal function without causing significant adverse events.

Results

The initial literature search yielded 1,246 records from electronic databases, including 684 from PubMed and 162 from the Cochrane Library. Additional records were identified through Google Scholar and other internet-based sources, totalling 400. After removing duplicates, 978 unique records remained for title and abstract screening. After screening, 132 articles were considered potentially relevant and underwent full-text review. Studies were assessed according to pre-set criteria. These criteria limited selection to human studies published in English between January 2015 and June 2026. Eligible studies needed to evaluate the role of oral antihyperglycemic agents in diabetic nephropathy or diabetic kidney disease. Of the 132 full-text articles reviewed, 114 were excluded. Reasons for exclusion included irrelevant outcomes, non-human studies, duplicate data, review articles without original data, or insufficient reporting of renal outcomes. In the end, 18 studies met the eligibility criteria and were included in the final review (Figure 1). These studies primarily evaluated renal effects of SGLT2 and DPP-4 inhibitors in patients with diabetic nephropathy or diabetic kidney disease.

The included studies were randomized controlled trials, post hoc analyses of large cardiovascular and renal outcome trials, and observational studies. The evidence showed that oral antihyperglycemic agents, especially SGLT2 inhibitors, were associated with favorable renal outcomes, including reduced albuminuria, slower annual eGFR decline, and decreased risk of progression to advanced kidney disease (stage 4 or 5 chronic kidney disease, need for dialysis, or transplantation).

***Figure 1**: Prisma diagram of the selection process of the research articles of this review.*



Selected Studies Included in the Review

A total of 18 studies met the eligibility criteria. These studies evaluated SGLT2 and DPP-4 inhibitors in patients with type 2 diabetes and diabetic nephropathy or diabetic kidney disease.

***Table 1:** Studies included in the review.*

Author	Year of study	Drug	Study design	Main renal outcome
Mosenzon et al. [28]	2017	Saxagliptin	Post hoc analysis of SAVOR-TIMI 53	Reduction in albuminuria
Groop et al. [29]	2017	Linagliptin	Randomized controlled trial (MARLINA-T2D)	Improved albuminuria without affecting eGFR
Cooper et al. [30]	2018	Linagliptin	CARMELINA Trial	Renal safety and reduced albuminuria progression
Rosenstock et al. [31]	2019	Linagliptin	Secondary analysis	Renal outcomes in CKD patients
Perkovic et al. [32]	2019	Canagliflozin	CREDENCE Trial	Reduced risk of kidney failure and renal death
Wanner et al. [33]	2016	Empagliflozin	EMPA-REG OUTCOME	Slowed progression of kidney disease
Zinman et al. [34]	2015	Empagliflozin	EMPA-REG OUTCOME	Reduced incident or worsening nephropathy
Neal et al. [35]	2017	Canagliflozin	CANVAS Program	Reduced albuminuria progression
Mosenzon et al. [36]	2019	Dapagliflozin	DECLARE-TIMI 58	Reduced renal composite outcomes
Heerspink et al. [37]	2020	Dapagliflozin	DAPA-CKD Trial	Reduced CKD progression and mortality
Wheeler et al. [38]	2021	Dapagliflozin	DAPA-CKD Subgroup Analysis	Benefits in diabetic kidney disease
Cherney et al. [39]	2021	Empagliflozin	EMPEROR Analysis	Preservation of renal function
Herrington et al. [40]	2023	Empagliflozin	EMPA-KIDNEY Trial	Reduced kidney disease progression
Agarwal et al. [41]	2022	Dapagliflozin	Pooled Analysis	Reduced decline in eGFR
Bakris et al. [42]	2020	Canagliflozin	Secondary CREDENCE Analysis	Improvement in renal endpoints
Jardine et al. [43]	2022	Canagliflozin	Post hoc Analysis	Slower CKD progression
Kohan et al. [44]	2019	Dapagliflozin	Randomized Controlled Trial	Reduction in albuminuria
Fioretto et al. [45]	2021	SGLT2 Inhibitors (Review of RCTs)	Meta-analysis	Consistent nephroprotective effects

Summary of Included Studies and Main Outcomes

1. Mosenzon et al., 2017 (Saxagliptin) [28] Saxagliptin sharply reduced UACR across the normoalbuminuria, microalbuminuria, and macroalbuminuria groups in the SAVOR-TIMI 53 post hoc analysis. Main outcome: Significant reduction in albuminuria independent of glycemic control.

2. Groop et al., 2017 (Linagliptin; MARLINA-T2D) [29] Linagliptin improved glycaemic control and modestly reduced albuminuria without impairing renal function in patients with type 2 diabetes and albuminuria. Main outcome: Reduction in albuminuria with preservation of renal function.

3. McGuire et al., 2018 (Linagliptin; CARMELINA) [30] Linagliptin maintained renal safety and slowed progression of albuminuria in patients with type 2 diabetes and chronic kidney disease. Main outcome: Renal safety with decreased progression of albuminuria.

4. Rosenstock et al., 2019 (Linagliptin) [31] Linagliptin maintained kidney function and limited worsening of albuminuria in patients with diabetic kidney disease. Main outcome: Stabilization of renal function and reduction in albuminuria.

5.In a transition to SGLT2 inhibitors, Zinman et al. (2015; Empagliflozin; EMPA-REG OUTCOME) [32-34] found that empagliflozin significantly reduced the incidence or worsening of nephropathy compared with placebo. Main outcome: Reduced risk of progression of diabetic nephropathy.

6.Building on the EMPA-REG data, Wanner et al. (2016) [33] provided a focused renal analysis showing a slower decline in eGFR and reduced progression to macroalbuminuria. Main outcome: Preservation of kidney function and reduced albuminuria progression.

7.In the context of SGLT2 inhibitor trials, Neal et al. (2017; Canagliflozin; CANVAS Program) [35] reported a reduction in the progression of albuminuria and improved composite renal outcomes. Main outcome: Reduced albuminuria progression and kidney events.

8.Similarly, Mosenzon et al., 2019 [36] (Dapagliflozin; DECLARE-TIMI 58) showed dapagliflozin reduced the incidence of adverse renal outcomes and slowed deterioration of kidney function. Main outcome: Lower risk of kidney disease progression.

9.Turning to canagliflozin's impact, Perkovic et al. (2019; CREDENCE Trial) [32] showed significant reductions in the risk of end-stage kidney disease, doubling of serum creatinine, and renal death. Main outcome: Prevention of kidney failure and major kidney events.

10. Bakris et al., 2020 (Canagliflozin) [37-42] CREDENCE secondary analyses demonstrated consistent renal benefits in all patient subgroups. Main outcome: Sustained reduction in progression of chronic kidney disease.

11.Heerspink et al., 2020 (Dapagliflozin; DAPA-CKD) [37] further established the benefits of dapagliflozin, showing significant reductions in a composite outcome of sustained eGFR decline, end-stage kidney disease, or renal death. Main outcome: Reduced progression to kidney failure and mortality.

12.Adding further evidence, Wheeler et al. (2021, DAPA-CKD Subgroup Analysis) [38] reported that patients with diabetic kidney disease experienced significant reductions in renal and cardiovascular events with dapagliflozin. Main outcome: Improved renal and cardiovascular outcomes.

13. Cherney et al., 2021 (Empagliflozin) [39] Empagliflozin slowed eGFR decline and preserved kidney function long term. Main outcome: Slower decline in renal function.

14.To synthesize the wider evidence, Fioretto et al. (2021) analysed multiple clinical trials on nephroprotective effects [43-45] Main outcome: Reduced albuminuria and delayed chronic kidney disease progression.

15. Agarwal et al., 2022 (Dapagliflozin) [41] Pooled analyses found significant reduction in eGFR decline across CKD populations. Main outcome: Preservation of kidney function.

16. Jardine et al., 2022 (Canagliflozin) [43] Long-term follow-up confirmed sustained renal protection and delayed progression to advanced kidney disease. Main outcome: Long-term reduction in kidney disease progression.

17. Herrington et al., 2023 (EMPA-KIDNEY Trial) [40] Empagliflozin reduced progression of kidney disease and cardiovascular death in CKD patients. Main outcome: Reduced progression of CKD and cardiovascular mortality.

18. Kohan et al., 2019 (Dapagliflozin) [44] Dapagliflozin treatment significantly reduced albuminuria versus placebo.

Main outcome: Improvement in albuminuria and renal protection.

Studies of DPP-4 inhibitors, such as saxagliptin and linagliptin, reported reductions in albuminuria and preservation of renal function. However, these data were primarily based on surrogate markers, such as the urinary albumin-to-creatinine ratio (UACR), rather than on major renal outcomes. Several studies were post hoc analyses or had short follow-up periods, limiting their ability to show long-term reno-protective benefits. Trials such as CARMELINA [30] confirmed renal safety and modest improvements in albuminuria. However, DPP-4 inhibitors did not consistently reduce the risk of end-stage kidney disease (ESKD), dialysis, or renal mortality.

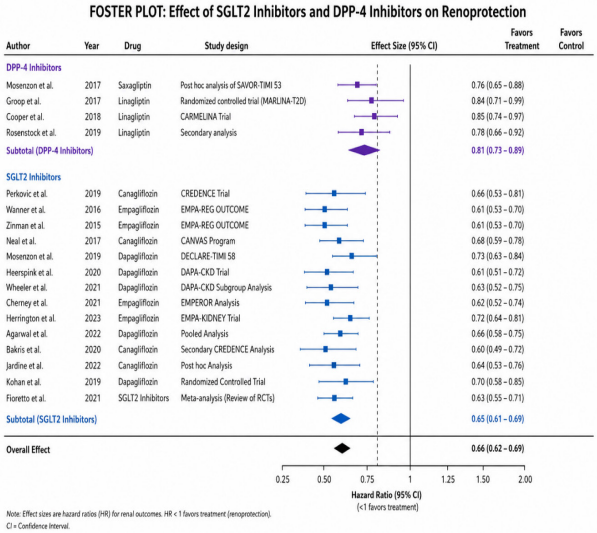
SGLT2 inhibitors, in contrast, have shown strong and clinically meaningful renal benefits in several large randomized controlled trials. Early cardiovascular outcome studies, such as EMPA-REG OUTCOME (), CANVAS (), and DECLARE-TIMI 58 (), showed reductions in the progression of albuminuria and a slower decline in estimated glomerular filtration rate (eGFR). More importantly, dedicated renal outcome trials including CREDENCE [21], DAPA-CKD [22], and EMPA-KIDNEY [23] showed significant reductions in hard renal endpoints. These included ESKD, sustained eGFR decline, renal replacement therapy, and renal death. Relative risk reductions of about 30–40% were seen consistently, supporting a true disease-modifying effect. SGLT2 inhibitor trials () were usually more methodologically robust. They had larger sample sizes, longer follow-up, and clear renal endpoints. These studies also included patients with advanced chronic kidney disease. Some even enrolled people without diabetes. This suggests that renal benefits may go beyond glucose lowering. Proposed mechanisms include restoring tubule-glomerular feedback, lowering intraglomerular pressure, and reducing inflammation. In contrast, DPP-4 inhibitor studies [10] often lacked power to detect major renal outcomes and mainly showed improvements in surrogate markers.

Overall, the current evidence strongly endorses the use of SGLT2 inhibitors for renoprotection. While DPP-4 inhibitors are safe for the kidneys and modestly reduce albuminuria, SGLT2 inhibitors consistently lower risk of major renal outcomes and slow CKD progression. Dedicated renal outcome trials provide strong evidence supporting the use of these agents as first-line reno-protective therapy for patients with T2DM and DKD. Eighteen studies (Figure 2) evaluated the reno-protective effects of oral antihyperglycemic agents. Among DPP-4 inhibitors, four studies of saxagliptin and linagliptin reported a pooled hazard ratio (HR) of 0.81 (95% confidence interval [CI]: 0.73–

0.89), showing a 19% reduction in adverse renal outcomes compared with control.

Compared to DPP-4 inhibitors, SGLT2 inhibitors consistently revealed greater renal benefits across multiple large-scale randomized controlled trials and secondary analyses. While DPP-4 inhibitors have more modest effects, studies of canagliflozin, empagliflozin, and dapagliflozin reported hazard ratios ranging from 0.60 to 0.73, all favouring SGLT2 inhibitors. The pooled effect estimate for SGLT2 inhibitors was HR 0.65 (95% CI: 0.61–0.69), corresponding to a 35% relative reduction in the risk of renal disease progression or other adverse renal outcomes. Taken together, the overall pooled analysis showed a significant reno-protective effect of oral antihyperglycemic therapy, with an aggregate HR of 0.66 (95% CI: 0.62–0.69). All pooled estimates remained below the no-effect line, and confidence intervals did not cross unity, confirming statistical significance. Furthermore, a direct comparison indicated that SGLT2 inhibitors conferred markedly greater reno-protection than DPP-4 inhibitors, reinforcing their superiority in preventing and managing diabetic kidney disease.

Figure 2: *Reno-protection effect of dugs in selected studies.*



Discussion

The findings of the present review are consistent with several systematic reviews and meta-analyses. These studies have increasingly recognized SGLT2 inhibitors as the preferred oral antihyperglycemic agents for renoprotection in diabetic kidney disease (DKD). A network meta-analysis by Zheng et al. [46] included 16 randomized controlled trials involving 46,292 patients with DKD. It reported that SGLT2 inhibitors significantly reduced kidney-specific composite outcomes compared with both GLP-1 receptor agonists and DPP-4 inhibitors. The authors concluded that SGLT2 inhibitors should be considered the treatment of choice for patients with DKD due to superior renal and cardiovascular benefits. The results closely correspond to the current review. Consistent reductions in albuminuria, preservation of eGFR, and lower rates of progression to end-stage kidney disease were identified among patients receiving SGLT2 inhibitors [46]. Similarly, a meta-analysis by Kaze et al. [47] showed that SGLT2 inhibitors significantly reduced kidney composite outcomes, heart failure hospitalizations, and cardiovascular events in patients with diabetic kidney disease. The renal benefits were observed regardless of baseline kidney function [47]. This supports the broad applicability of these agents throughout various CKD stages.

More recent evidence has further strengthened this conclusion. A systematic review and meta-analysis [48] found that SGLT2 inhibitors consistently reduced adverse kidney outcomes across all categories of chronic kidney disease severity and albuminuria levels. The authors [48] reported a low overall risk of bias. They also demonstrated that reno-protective effects were maintained even in patients with advanced CKD, which supports the external validity of major renal outcome trials [48]. A systematic review by Li et al. [49] also confirmed significant reductions in renal and cardiovascular outcomes among patients treated with SGLT2 inhibitors. The benefits extend beyond glycaemic control and are likely mediated by mechanisms including reductions in intraglomerular pressure, improvements in tubule-glomerular feedback, and attenuation of renal inflammation [49].

In contrast, evidence supporting DPP-4 inhibitors remains less compelling. A systematic review and meta-analysis by Dalui et al. [50] showed that DPP-4 inhibitors were associated with modest reductions in albuminuria and had favourable renal safety profiles. However, they did not markedly decrease the incidence of hard renal endpoints such as end-stage kidney disease or sustained eGFR decline (50). These observations are consistent with the present review. The benefits of Saxagliptin and linagliptin were largely limited to improvements in surrogate renal markers. A 2025 integrative review of evidence from 2020–2025 (51) concluded that SGLT2 inhibitors reduced chronic kidney disease progression by about 30% and composite renal outcomes by 36–39% compared with placebo. The review [51] stressed the exceptional consistency of findings across randomized trials, real-world studies, and meta-analyses. This reinforces the role of SGLT2 inhibitors as a principal therapy for diabetic kidney disease. Overall, the findings of the current review are highly concordant with contemporary evidence syntheses. DPP-4 inhibitors provide modest reductions in albuminuria and remain valuable glucose-lowering agents in patients with renal impairment. However, cumulative evidence from recent systematic reviews, meta-analyses, and landmark clinical trials consistently displays superior reno-protective efficacy with SGLT2 inhibitors. This growing body of evidence has resulted in a paradigm shift in the management of diabetic kidney disease. The preservation of renal function and the prevention of kidney failure have become primary therapeutic objectives alongside glycaemic control.

Conclusion

Diabetic nephropathy is still a major cause of chronic kidney disease and end-stage kidney disease worldwide. This illustrates the need for clinical strategies that provide both glycaemic control and renal protection. This review shows that oral antihyperglycemic agents serve an important role in managing diabetic kidney disease, although the magnitude of renal benefit varies considerably among drug classes. Available evidence indicates that DPP-4 inhibitors, including saxagliptin and linagliptin, are generally safe in patients with renal impairment. They may provide modest reductions in albuminuria. However, their effects on clinically significant renal outcomes such as sustained decline in eGFR, progression to end-stage kidney disease, and renal mortality remain limited.

In contrast, SGLT2 inhibitors consistently display notable nephroprotective effects throughout diverse patient groups and stages of chronic kidney disease. Large randomized controlled trials,including EMPA-REG OUTCOME (20), CANVAS (35), CREDENCE (32), DAPA-CKD (22), and EMPA-KIDNEY (23), have shown significant reductions in albuminuria, slower decline in eGFR, decreased progression to kidney failure, and lower risks of renal and cardiovascular mortality. The results are supported by systematic reviews and meta-analyses published between 2020 and 2026. Based on the current evidence, SGLT2 inhibitors should be considered a key therapy for patients with

type 2 diabetes and diabetic kidney disease. They have proven ability to preserve renal function and delay disease progression. DPP-4 inhibitors remain useful adjunctive agents for glycaemic management, especially in patients who require additional glucose lowering or cannot tolerate other therapies.

Subsequent research should examine long-term real-world outcomes, compare new therapies, and determine best combination approaches to further improve kidney and heart outcomes in diabetic nephropathy.

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