Review

Efficacy and Safety of Oral Antidiabetic Drugs in People with Diabetes and Chronic Kidney Disease: A Systematic Review

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This study is a systematic review assessing the efficacy and safety of oral antidiabetic drugs in managing type 2 diabetes mellitus in people with chronic kidney disease (CKD), focusing on their dosing and effects on renal function and glycemic control.

A systematic search of online databases was conducted for published from January 2023 to September 2024. Studies that focused on oral antidiabetic drugs for individuals with diabetes and CKD, and reported outcomes such as glycemic control, renal function, and adverse events were included. A risk-of-bias assessment was performed to evaluate study quality.

A total of 21 studies that met the criteria were included. The evidences indicate that SGLT2 (Sodium-Glucose Cotransporter-2) inhibitors and GLP-1 (Glucagon-like peptide-1) receptor agonists provide renal protective benefits. SGLT2 inhibitors are more effective especially in early-stages of CKD. DPP-4 (Dipeptidyl peptidase 4) inhibitors are safe across various CKD stages and require minimal dose adjustments. Metformin remains a popular drug for glycemic control but should be monitored and even discontinued in advanced stages of CKD because of the risk of lactic acidosis. Sulfonylureas were related to hypoglycemia risk.

Oral antidiabetic drugs, especially SGLT2 inhibitors and GLP-1 receptor agonists, are suggested in managing blood glucose in CKD patients owing to their renal and cardiovascular benefits. Individualized therapy is an important factor as drug safety and efficacy are influenced by CKD stage, comorbid conditions, and hypoglycemia risk. Individualized therapy helps maximize renal and cardiovascular protection while minimizing adverse outcomes. Regular monitoring of HbA1c (hemoglobin A1c), GFR (glomerular filtration rate), and albuminuria is recommended.

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INTRODUCTION

Chronic kidney disease (CKD) and type 2 diabetes mellitus (T2DM) are two global health burdens that frequently coexist, and diabetic patients are at risk of developing CKD worldwide.[1] According to recent epidemiological studies, nearly 40% of people with T2DM eventually develop CKD.[2] Although this systematic review focuses on studies published between 2023 and 2024, earlier references are included here to provide essential background on disease mechanisms, epidemiology, and treatment evolution. The presence of both diseases creates a cycle, where poor controlled diabetes leads to kidney damage, and declining

kidney function worsens metabolic dysregulation, including impaired glucose control, insulin resistance, and disturbances in lipid and electrolyte balance.[1,2] In people with T2DM, hyperglycemia leads to glomerular hyperfiltration, increased renal workload, and eventually kidney damage like glomerulosclerosis and tubulointerstitial fibrosis.[3,4]

As both CKD and T2DM progress, the risk of developing CVD (cardiovascular disease) increases, making CVD the leading cause of death in this population.[5-7] CKD and T2DM share common pathological mechanisms, such as inflammation, oxidative stress, and endothelial dysfunction, which accelerate atherosclerosis, hypertension, and heart failure.[8] Diabetic nephropathy, a major complication of T2DM, significantly increases the risk of cardiovascular events, including myocardial infarction and peripheral artery disease.[5,7] Moreover, CKD itself independently increases cardiovascular risk through mechanisms like fluid overload, altered calcium-phosphate metabolism, and activation of the renin-angiotensin-aldosterone system (RAAS), further complicating the clinical situation.[5,9]

The treatment of patients with diabetes and CKD is complicated due to the progressive nature of both diseases and the limited therapeutic options available.[4] Furthermore, treating one condition often affects the management and progression of the other.[1,4] Therefore, effective treatment strategies for diabetic patients with CKD are important not only to manage blood glucose levels but also to delay the progression of kidney damage.[6] For instance, traditional antidiabetic medications such as metformin and insulin require dose adjustments or discontinuation as kidney function declines.[1]

The choice of treatment regimen must be individualized, considering the patient's renal function and other comorbid conditions such as cardiovascular disease, hypertension, and heart failure, which often coexist with CKD.[10] In recent years, newer classes of medications, such as Sodium-Glucose Cotransporter-2 inhibitors (SGLT2) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have shown significant renal benefits.[11,12] SGLT2 inhibitors have been found to reduce the progression of CKD and decrease the risk of hospitalization for heart failure in people with T2DM.[11] These agents work by reducing glucose reabsorption in the kidneys, thereby improving glycemic control and exerting protective effects on the kidneys, such as reducing intraglomerular pressure and albuminuria.[13] Furthermore, GLP-1 RAs not only help control glycemic level but have also been associated with cardiovascular and renal benefits, making them a valuable option for patients with CKD.[12]

In addition to pharmacological interventions, lifestyle modifications, including dietary changes and regular physical activity, are essential in managing both CKD and T2DM.[4,14] Limiting dietary sodium and adopting a healthy diet can reduce hypertension and the risk of kidney damage.[14] Additionally, glycemic targets must be individualized, particularly in patients with advanced CKD, to prevent hypoglycemia while achieving acceptable glycemic levels.[15]

Treatment response in CKD patients is typically assessed using a combination of glycemic control and renal function markers.[2] Conventional glycemic control markers, such as hemoglobin A1c (HbA1c), are commonly used, but their accuracy can be less reliable in CKD patients due to altered red blood cell turnover and anemia, which is prevalent in CKD.[2,16] Therefore, alternative methods such as continuous glucose monitoring (CGM) systems are being used increasingly to assess glucose variability and prevent hypoglycemia in these patients.[2]

Renal function is routinely monitored using serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria.[6,17] The progression of kidney disease in diabetic patients can be slowed by targeting these markers, mostly through the use of agents like SGLT2 inhibitors and ACE inhibitors that have been shown to reduce proteinuria and slow GFR decline.[13,17]

This article reviews the problems in managing T2DM in patients with renal impairment, the preferred oral agents, evaluating their risks and benefits, new therapies with renal protective effects, and the importance of close monitoring to prevent adverse effects and disease progression.

MATERIALS AND METHODS

Study Design

This systematic review is conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines.[18] The study aims to on evaluate the efficacy and safety of oral glucose-lowering medications for

the treatment of diabetic patients with CKD.

Eligibility Criteria

This review included studies containing original data which evaluated the use of oral antidiabetic drugs in patients with CKD. The study population consisted of adults with diabetes at different stages of CKD (ranging from stage 1 to stage 5, including those with end-stage kidney disease (ESKD)). The included studies examined the effects of oral antidiabetic drugs, such as metformin, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, and thiazolidinediones. Studies which used combination therapies were also considered, if oral medications played a major role in the treatment regimen. Also, there were some comparisons with placebo or non-oral treatments (such as insulin). The primary outcome focused on glycemic control, defined as the management of blood glucose levels to achieve target HbA1c while minimizing hypoglycemia and addressing glucose variability. This was assessed primarily through HbA1c levels, and in some studies by continuous glucose monitoring (CGM) or glycated albumin. Secondary outcomes included kidney disease progression (defined as decline in estimated glomerular filtration rate (eGFR), onset of end-stage renal disease (ESRD), or development of albuminuria), cardiovascular complications, overall mortality, and episodes of hypoglycemia (Assessed in terms of both prevalence and severity ranging from mild events to severe events requiring medical assistance).

Study Selection

The study selection process was performed by the reviewers. First, titles and abstracts screened to identify potentially relevant studies. The initial screening yielded approximately 130 articles. The full texts of these articles were then retrieved and evaluated based on the inclusion and exclusion criteria. Discrepancies were resolved by consultation with other reviewers. Finally, 21 articles were met the criteria for inclusion. Figure 1 demonstrates the PRISMA flowchart of this systematic review.

Inclusion and Exclusion Criteria

For this review, studies were considered if they assessed the outcomes of oral antidiabetic agents among diabetic patients at varying stages of chronic kidney disease (CKD) stages. Eligible study designs were both randomized controlled trials (RCTs) and observational studies, provided that they reported original data. Combination therapies were also included in studies if the oral agents constituted the predominant treatment regimen. Studies were excluded if they addressed only gestational diabetes,

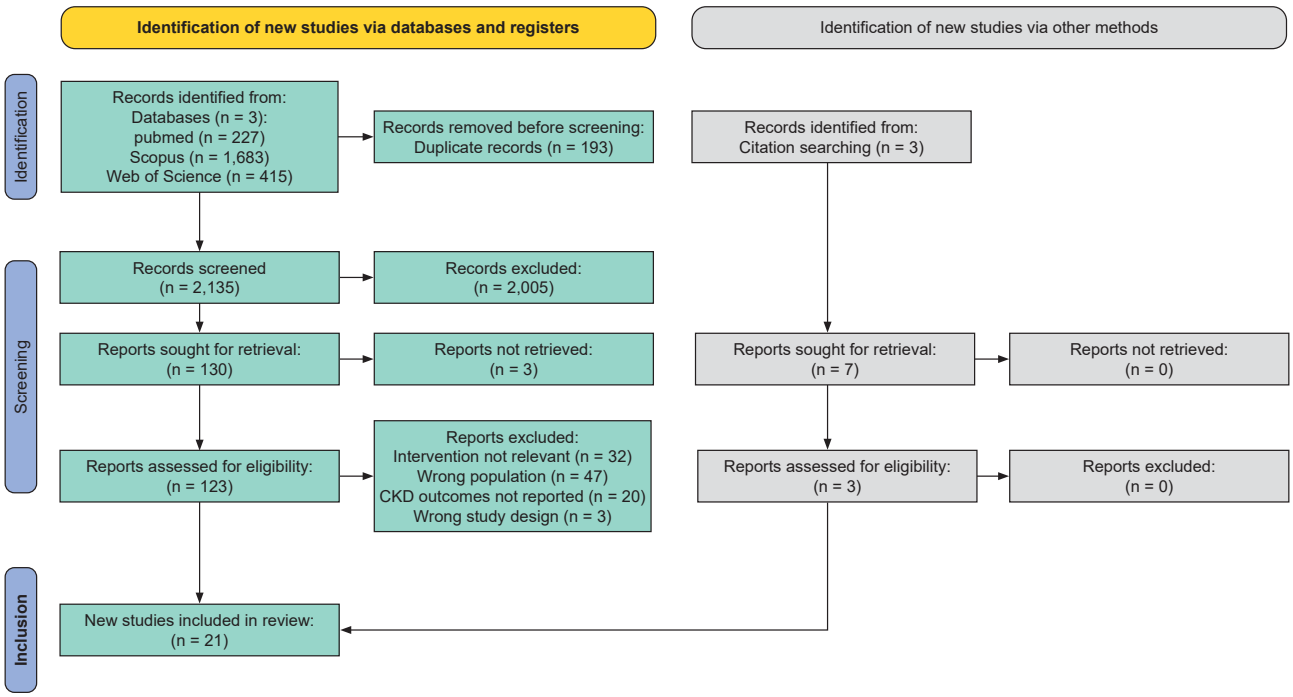

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources

included participants without CKD, or did not report specific CKD-related outcomes.

Search Strategy

We searched across several databases, including PubMed, Scopus, Web of Science, and Google Scholar, using Medical Subject Headings (MeSH) and relevant keywords. The search terms included "Diabetes Mellitus," "chronic kidney disease" (or 'CKD" or "Renal Insufficiency"'), "Antidiabetic Drugs" (or specific agents like "Metformin," "DPP-4 inhibitors," and "SGLT-2 inhibitors"), "Type 2 Diabetes," and "renal disease." The search covered articles published between January 2023 and September 2024, and we considered studies in English. Additionally, we manually searched reference lists from related reviews and articles to identify more relevant studies. A complete list of search terms, comprising keywords and MeSH terms, can be found in Table S2 in the supplementary file.

Risk of Bias Assessment

To ensure the quality and reliability of the included studies, we evaluated randomized controlled trials (RCTs) using Cochrane RoB 2 and observational studies with the Newcastle–Ottawa Scale (NOS) according to the classification updated in the provided uploaded guideline. For RCTs, allocation and blinding were sufficiently explained with adjudication of clinical endpoints and therefore low risk of bias in most domains. However, secondary or subgroup analyses were considered as raising "some concerns" regarding selective reporting when outcomes or subgroups were neither fully prespecified. Observational studies (propensity-matched or claims-based cohorts) attained good NOS quality generally with rigorous exposure ascertainment and proper adjustment, although residual confounding cannot be ruled out and comparability was the most common limitation. Complete assessments are shown in Supplementary Tables.

Two independent reviewers managed the bias assessment. Disagreements were resolved through discussion to reach a consensus. This process ensured evaluation of potential bias in the included studies.

Ethical Considerations

As this is a systematic review of published studies, no ethical approval was applicable. However, we adhered to ethical research practices by citing all sources and using established methodologies for unbiased data extraction and analysis.

CKD Classification and its Relevance in T2DM Management

The KDIGO 2023 guidelines classify CKD using both estimated glomerular filtration rate (eGFR) and albuminuria levels, which together reflect disease severity and risk of progression.[19] eGFR categories range from G1 (normal or high, ≥90 mL/min/1.73 m²) to G5 (kidney failure, < 15 mL/min/1.73 m² or on dialysis), while albuminuria is categorized as A1 (normal to mildly increased, < 30 mg/g), A2 (moderately increased, 30–300 mg/g), and A3 (severely increased, > 300 mg/g).[19] Patients with lower GFR and higher albuminuria have more advanced CKD and worse prognosis.[20] These classifications are essential not only for staging CKD but also for guiding the management of type 2 diabetes mellitus (T2DM) in this population.

Importantly, drug selection in T2DM must be according to CKD stage for each patient. For example, metformin is considered safe in G1–G3a but should be reduced at eGFR < 45 mL/min/1.73 m² and discontinued in G4–G5 because of the risk of lactic acidosis.[21,22] SGLT2 inhibitors retain renal and cardiovascular in an eGFR as low as G3b and

Table 1. Discontinue level and dosing of popular drugs

Name of the drug	Discontinue level	Dose
Dapagliflozin	GFR<25 (Glomerular filtration rate)	10 mg
Empagliflozin	GFR<30	10-25 mg
Gliclazide	GFR<30	40-320 mg
Linagliptin	No dose adjustment needed = 5 mg	
Sitagliptin	GFR<25	25-100 mg
Metformin	GFR<30	500-3000 mg

in some cases to eGFR 20 mL/min/1.73 m², but should be discontinued when dialysis is initiated (G5).[23] DPP-4 inhibitors are generally safe across CKD stages, though some of them require dose adjustments (e.g., sitagliptin), while linagliptin does not.[24-26] Sulfonylureas can be used in early CKD but have a higher risk of hypoglycemia in G3b–G5 stages.[21] Thiazolidinediones do not require renal dose adjustment but are limited in advanced CKD due to the fluid retention risk.[25] Linking CKD stage with drug dosing helps optimize glycemic targets, typically < 7% HbA1c for most non-pregnant adults, with more relaxed targets (e.g., < 8%) in patients with limited life expectancy or higher hypoglycemia risk.[27] Achieving appropriate glycemic control reduces the incidence of microvascular complications, including albuminuria and nephropathy progression.[20]

Efficacy and safety of oral antidiabetic drugs in diabetes and CKD

Managing blood glucose levels in CKD patients with T2D needs a careful approach to avoid worsening renal function. This review discusses the efficacy and safety of different classes of oral antidiabetic drugs, with a focus on their impact on glycemic markers like HbA1c, and renal function indicators like GFR and urinary albumin-to-creatinine ratio (UACR). Knowing the effects of each drug class on both glycemic control and kidney function is important for improving treatment in these patients while minimizing the risk of complications.

Sodium-Glucose Cotransporter-2 Inhibitors

SGLT2 inhibitors are an important key in managing patients with T2D and CKD due to their unique mechanism of increasing glucosuria, reducing hyperglycemia, and demonstrating renal protective properties (even compared to glucagon-like peptide-1 receptor agonists (GLP-1Ras)).[24,28,29] These drugs include canagliflozin, dapagliflozin, empagliflozin, and sotagliflozin, each with distinct benefits for diabetic patients with renal impairment.[24] Empagliflozin was found to activate the tubuloglomerular feedback (TGF) mechanism, a process that helps regulate kidney filtration. This activation leads to a reduction in glomerular hyperfiltration, a key factor in preventing kidney damage in CKD.[30] Additionally, SGLT2 inhibitors offer cardioprotective effects by blocking the sodium-hydrogen exchanger (NHE), reducing intracellular sodium and calcium levels, thereby decreasing oxidative stress and inflammation, and limiting cardiac cell apoptosis.[31]

SGLT2 inhibitors were found to reduce the annual decline in eGFR by 1.41 mL/min/1.73 m² per year. The safe usage of SGLT2 inhibitors was noted even in patients with moderate renal impairment, with observed positive effects across various age groups.[32]

Canagliflozin

Safe Dose and Usage. Canagliflozin has been extensively studied in patients with moderate CKD, especially in the CREDENCE trial. It helped to reduce the risk of major kidney outcomes by slowing the progression of CKD.[24,27,29] Canagliflozin is typically prescribed at a dose of 100 mg daily, but it should be discontinued if eGFR falls below 30 mL/min/1.73 m².[24,27] the drug's effect was more obvious in patients with higher HbA1c.[27]

Effect on Laboratory Findings. Canagliflozin significantly reduces albuminuria and preserves kidney function.[24,27,29,33] Post-hoc analyses of CREDENCE trial showed that, compared to placebo, canagliflozin reduced annual eGFR decline by 1.52 mL/min/1.73 m²/year (95% CI 1.11–1.93) and lowered UACR by 31% (95% CI 27–35), with consistent benefits across HbA1c strata (greater absolute slope benefit at higher HbA1c).[27] It is noteworthy to mention that canagliflozin's glucose-lowering effect diminishes as eGFR declines.[24]

Dapagliflozin

Safe Dose and Usage. Evidence from DAPA-CKD trial showed that dapagliflozin is effective in reducing kidney disease progression and cardiovascular events in patients with CKD.[28,34] Dapagliflozin is typically prescribed at 10 mg daily and should be discontinued when eGFR drops below 25 mL/min/1.73 m².[28,29,34] This drug also reduced the initiation of insulin (HR 0.72, 95% CI 0.54–0.96) compared to placebo.[34]

Effect on Laboratory Findings. Dapagliflozin helped HbA1c reduce about 4.4-5.5 mmol/mol (0.4-0.5%) in patients with CKD, with benefits on blood sugar control even in later levels of CKD.[29] It also slows the progression of renal disease by preserving eGFR and reducing proteinuria.[28,29,33,34]

This effect was seen in all agents of SGLTs, and also including those on insulin, sulfonylureas, or DPP-4 inhibitors.[34]

Empagliflozin

Safe Dose and Usage. The EMPA-KIDNEY trial demonstrated that empagliflozin slows CKD progression and reduces cardiovascular mortality.[20,28,35] It can be used safely in patients with eGFR as low as 30 mL/min/1.73 m² at a dose of 10 mg daily, though renal function should be regularly monitored.[20,35] The combination of empagliflozin (initial dose of 10 mg once daily, titratable to 25 mg if fasting blood glucose levels were ≥100 mg/dL) and linagliptin (5 mg daily) was evaluated and empagliflozin was generally well-tolerated, with no significant adverse events over the 12-week treatment period.[20,23]

Effect on Laboratory Findings. Empagliflozin demonstrates renoprotective effects as indicated by reduced urinary biomarkers such as UACR.[35] Empagliflozin produced an acute ~2.1 mL/min/1.73 m² dip (first 2 months) and then halved the chronic eGFR slope from −2.75 to −1.37 mL/min/1.73 m²/year (relative 50% improvement; 95% CI 42–58).[35] Also, it led to a significant reduction in glycemic parameters such as HbA1c and FBS.[23,33]

Sotagliflozin

Safe Dose and Usage. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, offers benefits in patients with T2D and CKD.[36] SCORED trial showed that sotagliflozin reduced cardiovascular events and improved renal outcomes at doses of 200-400 mg daily.[36,37] Sotagliflozin was generally well tolerated, with adverse events similar to the placebo group. However, there is a risk of genital infections and volume depletion.[36,37] Another study targeted people with CKD stages 2-3, with an eGFR range of 25–60 mL/min/1.73 m². The drug was generally well-tolerated within this patient population as well.[37]

Effect on Laboratory Findings. CKD stage 3 RCT (26 weeks): HbA1c LS-mean difference vs placebo −0.20% (95% CI −0.40 to −0.09) at 26 weeks (400 mg); more participants achieved HbA1c < 7% (+7.4%, 95% CI 1.1–13.7).[36] Albuminuria fell by about 31–39% versus placebo at weeks 14–26 but these differences were not sustained at week 52. Severe hypoglycaemia was 0.8% (placebo), 0.4% (200 mg), 1.2% (400 mg).[36]

SCORED (lab-data analysis). vs placebo, the composite ≥50% eGFR decline, eGFR < 15, dialysis, or transplant: HR 0.62 (95% CI 0.48–0.82); the broader cardiorenal composite (adds CV/kidney death): HR 0.77 (95% CI 0.65–0.91). AKI risk: RR 0.90 (95% CI 0.70–1.00).[37]

Ertugliflozin

Safe Dose and Usage. In the VERTIS-CV trial, participants received once-daily ertugliflozin 5 mg or 15 mg or placebo in addition to background therapy. The trial excluded individuals with eGFR < 30 mL/min/1.73 m².[38] Overall safety was similar to placebo across age subgroups, with no differences in kidney-related adverse events or hypoglycemia rates by treatment within age groups.[38]

Effect on Laboratory Findings. Compared with placebo, ertugliflozin showed benefits for kidney endpoints across age groups. For the prespecified kidney composite including doubling of serum creatinine, the hazard ratio (HR) was 0.84 (95% CI 0.60–1.17) in participants ≥65 years and 0.78 (95% CI 0.55–1.10) in those < 65 years. For the prespecified exploratory kidney composite (sustained ≥40% eGFR decline, dialysis or transplant, or kidney death), the HR was 0.71 (95% CI 0.47–1.09) in ≥65 years and 0.62 (95% CI 0.43–0.91) in < 65 years.[38] eGFR curves displayed the typical initial dip followed by stabilization, with the final eGFR at week 260 being higher in the ertugliflozin group than in placebo. Furthermore, increases in UACR overtime were smaller with ertugliflozin.[38]

Enavogliflozin

Safe Dose and Usage. Enavogliflozin, a SGLT2 inhibitor, was studied at a dose of 0.5 mg daily.[39] The findings showed that using enavogliflozin did not significantly differ (systemic exposure (AUC) was not significantly correlated with creatinine clearance (CrCl) (single-dose r = 0.18, P = .42), although Cmax decreased slightly with lower renal function) across different renal function groups.[39]

Effect on Laboratory Findings. The glucosuric effect of enavogliflozin was positively correlated with renal function: after single dose, r = 0.79 (P < .0001); after multiple doses, r = 0.66 (P = .044). Mean 24-hour urinary glucose excretion ($UGE_{0–24h}$) after a single dose increased by 76.72 g, 69.19 g,

17.61 g, and 4.16 g in normal, mild, moderate, and severe renal impairment (RI) groups, respectively. At steady state in multiple doses the values were 76.64 g in those with normal function and 33.80 g in those with moderate impairment.[39]

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 inhibitors, including sitagliptin, alogliptin, saxagliptin, and linagliptin, are preferred in patients with CKD due to their favorable renal safety.[24] These drugs have moderate glucose-lowering effects and do not require for major dose adjustments across different levels of kidney function, making them a practical choice for CKD patients. Even a study showed a decline in eGFR.[24,26]

Linagliptin

Safe Dose and Usage. Unlike other DPP-4 inhibitors, linagliptin does not require dose adjustments for renal impairment, making it a suitable option for patients with CKD, even in those with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).[26]

In one study a daily dose of 5 mg was administered over 24 weeks for people with type 2 diabetes and diabetic nephropathy and no significant adverse effects like hypoglycemia or acute pancreatitis were observed.[26]

In another study, DPP-4 inhibitor use was associated with an improvement in albuminuria (OR 0.77, 95% CI 0.41–0.97) and was well tolerated and with positive effects.[23]

Effect on Laboratory Findings. A 24-week RCT of linagliptin in T2DM with microalbuminuria showed a higher proportion achieving improvement in UACR vs placebo (68.3% vs 25.0%, $P < .001$); however, changes in HbA1c, serum creatinine, and eGFR were not significantly different from placebo. This agent is particularly safe for CKD patients due to its minimal renal excretion.[23,26]

Sitagliptin

Safe Dose and Usage. Sitagliptin was used at a dose of 100 mg once daily in the study, with patients were categorized into two groups based on the treatment duration: less than one year (SL group) and more than one year (SM group to evaluate its long-term safety, efficacy, and potential for renal protection) and an active-comparator group received pioglitazone 30 mg once daily; a healthy control group was also included.[25] This allowed the study to compare the effectiveness and safety of short-term versus long-term treatment.[25]

Effect on Laboratory Findings. The study found that compared with pioglitazone, sitagliptin improved glycemic control, by reducing HbA1C and serum glucose levels, particularly in long-term usage (SM group).[25] Sitagliptin showed a reno-protective effect by lowering markers of renal injury and maintaining kidney function through improved creatinine levels and reduced urea and it also modulated the glyoxalase system, indicating reduced oxidative stress.[24,25] Sitagliptin's impact on LncMIAT suggests it may lessen renal tubular injury in T2DM people.[25]

BIGUANIDES

Metformin

Metformin remains the main management of T2DM but carries increased risks in advanced CKD due to the probability of lactic acidosis.[21,22]

Safe Dose and Usage. Metformin can be used safely in patients with an eGFR of 30-45 mL/min/1.73 m^2, but the dose should be reduced to a maximum of 1,000 mg per day. It is recommended to avoid in patients with eGFR < 30 mL/min/1.73 m^2 due to its potential risk for lactic acidosis.[21-23]

Effect on Laboratory Findings. One study found that metformin provided end-organ protection beyond glycemic control, as it was associated with slower eGFR decline and a reduced risk of kidney events or progression to end-stage renal disease (ESRD) compared to sulfonylureas. The risk of death and kidney event both in the first 360 days (adjusted HR 0.79, 95% CI 0.72–0.87) and from day 361 onward (adjusted HR 0.76, 95% CI 0.70–0.83). For kidney events alone, metformin was associated with a lower risk after day 361 (HR 0.73, 95% CI 0.59–0.91.[21] Consequently, patients using Patients using metformin experienced fewer kidney events and deaths compared to those on sulfonylureas especially after day 361.[21] There was a slight decline in eGFR, from 43.7 ± 18 mL/min/1.73 m^2 to 42 ± 18.3 mL/min/1.73 m^2, suggesting a gradual decrease in kidney function during the treatment period.[24] Also, Metformin users showed a mild worsening in albuminuria, However, this change was not statistically significant (UACR 345.1 ± 355.4 → 376.2 ± 401.8 mg/g, OR 0.98 (95% CI 0.33–1.75), $P = .12$.).[24]

Glucagon-Like Peptide-1 Receptor Agonists

GLP-1 RAs, including liraglutide, dulaglutide and semaglutide, are potent glucose-lowering agents with additional renal protective properties. These agents are primarily administered via injection, though an oral formulation of semaglutide is available.[28,32]

Semaglutide

Safe Dose and Usage. In PIONEER 5 study 14 mg of oral semaglutide was used in patients with type 2 diabetes and moderate renal impairment.[40]

Effect on Laboratory Findings. Oral semaglutide was shown to lower HbA1c by ~0.6–1.4%; renal laboratory outcomes are not numerically detailed in the included articles.[40]

Sulfonylureas

Sulfonylureas, including gliclazide and glimepiride, are widely used but are associated with a higher risk of hypoglycemia, especially in patients with impaired renal function.[21]

Safe Dose and Usage. Sulfonylureas should be used with caution in patients with CKD, particularly when eGFR < 30 mL/min/1.73 m². Gliclazide is often preferred due to its lower risk of hypoglycemia.[21]

Effect on Laboratory Findings. Patients on sulfonylureas experienced a small decline in eGFR. ACR increased from 388.8 ± 398.4 mg/g to 420 ± 440 mg/g, and the association with albuminuria worsening was not statistically significant (OR 1.65, 95% CI 0.77–2.45; *P* = .25).[24] Moreover, sulfonylureas were associated with higher mortality rates, reinforcing the importance of cautious use in patients with declining kidney function.[21]

Thiazolidinediones (TZDs)

Thiazolidinediones, such as pioglitazone, are generally not recommended in advanced CKD due to the risk of fluid retention and heart failure exacerbation.

Safe Dose and Usage. TZDs like pioglitazone (30 mg daily) should be avoided in patients with advanced CKD because they can exacerbate heart failure and potentially worsen renal function.[24,25]

Effect on Laboratory Findings. In a study, pioglitazone users showed a small eGFR decline (38.0 ± 13.6 to 37.2 ± 14.2 mL/min/1.73 m²) with a concomitant rise in serum creatinine (171.6 ± 57.6 to 186.0 ± 89.6 µmol/L).[24] Similarly, Albuminuria (spot UACR) changed only minimally (≈327 to ≈330 mg/g). Because UACR in that cohort was highly right-skewed (SD exceeded the mean), mean ± SD is not an appropriate summary; therefore, we do not interpret those SD values and instead rely on the study's effect estimate, which showed no statistically significant association between pioglitazone use and albuminuria change (OR 1.99; 95% CI 0.56–3.34; *P* = .50).[24] In terms of CKD progression, 20.0% of pioglitazone users showed rapid progression, 68.8% had no CKD stage change, and 11.1% improved.[24]

DISCUSSION

Here is a short review of the important drugs and their information.

Oral antidiabetic drugs are essential in managing blood glucose in people with diabetes and CKD, but their safety and effectiveness are dependent on the degree of renal impairment.[24,41]

SGLT2 inhibitors, such as canagliflozin, dapagliflozin, and empagliflozin, are the preferred type for CKD patients due to their benefits in glucose control and kidney protection in early stages by reducing glomerular hypertension (which is the primary cause of glomerular damage and proteinuria over time).[20,27,30,35] However, their glucose-lowering efficacy reduces as kidney function decreases, and they must be discontinued when eGFR falls below 25-30 mL/min/1.73 m².[24,27] An important benefit of using these drugs is that they support kidney function. Especially the combination of empagliflozin (which has a moderate potency) and linagliptin is a reasonable choice in people with GFR as low as 30 mL/min/1.73 m².[23,28]

GLP-1 receptor agonists, such as semaglutide, offer renal and cardiovascular benefits, making them appropriate for CKD patients, especially in the early to moderate stages.[32,40] They are usually injectable though oral forms of semaglutide are available. Despite their efficacy, their use may be limited by cost and gastrointestinal side effects.[28]

DPP-4 inhibitors are often preferred for their safety in CKD patients, especially linagliptin, which does not require dose adjustments for renal impairment.[26,41] They effectively reduce HbA1C and have minimal impact on eGFR or urinary creatinine, and they lack the strong renoprotective

effects seen with SGLT2 inhibitors and GLP-1 receptor agonists.[24,25]

Metformin remains a popular drug for managing T2DM in patients with mild to moderate CKD. It is suggested not to use in CKD (eGFR < 30 mL/min/1.73 m²) due to the risk of lactic acidosis.[21,23] Sulfonylureas and thiazolidinediones (TZDs), are effective at lowering blood glucose, but require caution in CKD because they are associated with elevated risks of hypoglycemia and fluid retention, respectively.[24,25]

While most of the included studies considered mostly monotherapies, some examined combination regimens. Günes-Altan *et al.* compared empagliflozin + linagliptin with metformin + insulin, stating that the initial decline in eGFR during SGLT2-based therapy was attributed to enhanced vascular compliance (ΔmGFR being associated with Δpulse-wave-velocity: r = 0.476; P = .005).[23] Chu *et al.* studied adults with CKD and T2DM already treated with an SGLT2 inhibitor and found that the adding a GLP-1 RA produced benefits over the addition of basal insulin. These comprised a larger decrease in HbA1c (−1.3 vs −1.1; P = .03), more weight loss (−3.4 kg vs +2.6 kg; P < .001) and a slower decline in eGFR (−0.3 vs −2.4 mL/min/1.73m²; P = .02), without increased hypoglycaemia, during the period after the addition.[40] In the study by Beernink *et al.* reported that dapagliflozin decreased kidney and cardiovascular event rates across various background classes and combinations of glucose-lowering therapies, without significant interaction based on type of therapy, and resulted in decreased initiation of insulin during the post-trial period (HR 0.72, 95% CI 0.54-0.96).[34] Collectively, these diverse results indicate that combination regimens are clinically pertinent and may offer additional benefit to select patients; nevertheless, current evidence is insufficient for a systematic comparative review of combinations versus monotherapies.

Although no studies from 2023–2024 evaluated repaglinide, we briefly mention it because older evidence (e.g., Marbury *et al.*, 2003) supports its safe use in patients with moderate-to-severe CKD. Its maximum safe dose is up to 4 mg three times daily, with titration to achieve glycemic control. However, its role has not been re-evaluated in recent clinical trials.[42]

In managing blood glucose in CKD patients, regular monitoring of HbA1c, eGFR, and urinary albumin is important to ensure safety and efficacy. Newer drugs like SGLT2 inhibitors and GLP-1 receptor agonists have significant renal benefits, but individualized therapy accompanied by careful monitoring are critical for optimizing patient outcomes and preventing further kidney damage.[24,29,41]

In practice, for individuals with progressive renal impairment who prefer to avoid insulin, a regimen combining Repaglinide (up to 4 mg), Empagliflozin (up to 10 mg), and Linagliptin (5 mg) is an effective choice. If this combination does not yield acceptable results, insulin therapy becomes the necessary option.

Limitations

This systematic review has several limitations that should be acknowledged. First, included studies varied in terms of design, population, and outcomes measures. While there were some large-scale randomized controlled trials employed strong study methods, others consisted of small-scale clinical trials, retrospective cohorts, or post hoc analyses, which could restrict comparability and create potential for bias. Second, follow-up periods varied in studies, and some trials focused short-term outcomes (e.g., 24–52 weeks), therefore restricting inferences to long-term oral antidiabetic drug effectiveness and safety in chronic kidney disease (CKD). Third, study populations often consisted of patients at various points in CKD, from early disease to end-stage renal disease, resulting in heterogeneity in treatment responses and therefore the generalizability. Fourth, outcome definitions varied; while some kidney disease progression was evaluated in terms of eGFR slopes or albuminuria, others made composite endpoints, such as ESRD, cardiovascular events, or mortality, thus restricting uniformity in portraying primary, treatment-related outcomes. Fifth, some included trials were secondary or exploratory analyses of larger cardiovascular outcome trials, meaning renal outcomes were not always prespecified or adequately powered. Finally, potential publication bias cannot be excluded, as ongoing or unpublished negative trials may not have been captured despite adherence to PRISMA guidelines. Future research should aim to address these gaps by conducting well-powered randomized controlled trials with longer follow-up, standardized endpoints,

and economic evaluations to determine cost-effectiveness and guide resource allocation.

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