Current Therapeutic Research 101 (2024) 100763

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Safety and Efficiency of Dipeptidyl Peptidase IV Inhibitors in Patients with Diabetic Kidney Disease: A Systematic Review and Meta-Analysis

Adili Tuersun, M.A.[1], Munire Mohetaer, M.A.[2], Guanxin Hou, B.A.[3], Gang Cheng, Ph.D[4,*]

[1] School of Life Sciences and Biopharmaceutics, Shenyang Pharmaceutical University, Shenyang, Liaoning, China
[2] School of Business Administration, Shenyang Pharmaceutical University, Shenyang, China
[3] Department of Pharmacy, General Hospital of Northern Theater Command, Shenyang, China
[4] Department of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China

ARTICLE INFO

Article history:
Received 3 June 2024
Accepted 30 September 2024

Key words:
Diabetic kidney disease
Dipeptidyl peptidase-4 inhibitors
Glomerular filtration rate
Urinary albumin-to-creatinine ratio
Estimated glomerular filtration rate

ABSTRACT

Background: To investigate the safety and efficiency of dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with diabetic kidney disease.
Methods: We conducted a comprehensive literature search across multiple databases, including Embase, PubMed, CNKI, and the Cochrane Central Register of Controlled Trials, from inception to January 2024. The search focused on randomized controlled trials (RCTs) that directly compared DPP-4 inhibitors with placebos or other glucose-lowering therapies. A meta-analysis was performed to pool data and quantify the therapeutic effects and safety profile of DPP-4 inhibitors in DKD.
Results: Twenty-three RCTs with 16,378 participants were included. DPP-4 inhibitors significantly reduced urinary albumin-to-creatinine ratio (UACR) and HbA1c levels compared to controls (UACR: SMD -0.23, 95% CI: -0.41, -0.06; $p = 0.01$; HbA1c: SMD -0.32, 95% CI: -0.51, -0.14; $p = 0.0006$). A higher proportion of patients in the DPP-4 inhibitor group achieved at least a 30% reduction in UACR (OR = 1.73, 95% CI: 1.10, 2.73; $p = 0.02$). However, estimated glomerular filtration rate (eGFR) and serum creatinine (SCr) changes were similar between groups (eGFR: $p = 1.00$; SCr: $p = 0.67$). No significant differences were found in all-cause mortality (OR = 0.94, 95% CI: 0.83, 1.06; $p = 0.31$) or hypoglycemia risk (OR = 1.10, 95% CI: 0.80, 1.52; $p = 0.54$) between the DPP-4 inhibitor and control groups.
Conclusions: DPP-4 inhibitors exhibit renoprotective properties, indicated by significant reductions in UACR and HbA1c levels. They do not appear to increase the risk of hypoglycemia, presenting a favorable safety profile when compared to placebo or alternative antidiabetic agents.

Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic condition characterized by hyperglycemia due to insulin deficiency/insensitivity and glucagon dysregulation.[1] Diabetic kidney disease (DKD), a common microvascular complication of T2DM, accounts for around one-third of end-stage renal disease (ESRD) cases globally.[2] DKD exhibits persistent albuminuria, deteriorating renal function, and subsequently leads to ESRD.[3,4] Hyperglycemia drives DKD progression through various pathways, including intracellular glucose utilization, glycation end product accumulation, oxidative stress, and epigenetic changes.[5] Effective glucose management has been shown to prevent the onset and progression of DKD.[6] However, the impact of different antidiabetic medications on kidney health varies.[7]

DPP-4 inhibitors are a class of antidiabetic agents that enhance the action of incretin hormones by inhibiting the breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[8] While studies have demonstrated the safety of DPP-4 inhibitors in patients with chronic kidney disease,[9] the impact of these inhibitors on renal outcomes remains inconsistent.[10] The efficacy of DPP-4 inhibitors in DKD has shown mixed results across RCTs. For example, the SAVOR-TIMI 53 trial demonstrated a significant reduction in UACR with saxagliptin treatment without affecting renal function.[11] Conversely, the TECOS trial observed a modest decrease in eGFR with sitagliptin treatment.[12] Research assessing the therapeutic benefits and safety of sitagliptin in the early stages of diabetic nephropathy revealed that

* Address correspondence to: Gang Cheng, Department of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China.
E-mail address: chenggang63@hotmail.com (G. Cheng).

https://doi.org/10.1016/j.curtheres.2024.100763

the medication effectively decreased albuminuria and enhanced blood sugar management. Additionally, it was found to be well-tolerated by individuals suffering from the initial phases of this kidney condition[13]. Further investigation indicates that in individuals with diabetic nephropathy, there was no notable variance in the average urinary albumin to creatinine ratio (UACR) or other clinical measures between those who received linagliptin and those who were given a placebo.[14] These discrepancies highlight the need for further investigation into the efficacy and safety of DPP-4 inhibitors in DKD.

Our study aims to fill the gaps in understanding the role of DPP-4 inhibitors in renal protection and glucose management for patients with DKD. We will conduct a comprehensive systematic review and meta-analysis of RCTs comparing DPP-4 inhibitors with placebo or other glucose-lowering agents in DKD patients. By integrating data from multiple studies, we will provide a more robust assessment of the therapeutic efficacy and safety profile of DPP-4 inhibitors in this vulnerable patient population.

Methods

This comprehensive review adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards[15] and has been carried out as per a preregistered protocol (PROSPERO registration number: CRD42024521277).

Search strategy and study selection

Our exhaustive search spanned multiple databases, including CNKI, Embase, PubMed, and the Cochrane Central Register of Controlled Trials, aiming to identify relevant RCTs published as full-text documents from the beginning of the record until January 2024, without imposing any language barriers. The targeted search criteria for DPP-4 inhibitors encompassed terms such as DPP-4 inhibitor, DPP4 inhibitor, alogliptin, anagliptin, evogliptin, gemigliptin, linagliptin, omarigliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin. Details of the search terms are provided in Supplementary Materials (Table 1S). A pair of researchers established the criteria for study selection and proceeded to review the titles and abstracts from the search outcomes, excluding any duplicates. Subsequently, the two authors Adili and Munire independently evaluated the full articles against the set criteria for eligibility. In cases of disagreement, a resolution was reached through mutual consensus, or a third reviewer was enlisted to make the final decision.

Our meta-analysis included RCTs based on the following specific criteria:

(1) The trials must have been randomized and controlled, comparing DPP-4 inhibitors to either placebo or active glucose-lowering medications.
(2) They had to involve adult patients diagnosed with diabetic kidney disease.
(3) A minimum follow-up duration of 8 weeks was required to ensure the sustainability of the findings.
(4) The trials had to report one or more renal outcomes, such as changes in urine albumin-to-creatinine ratio (UACR) or estimated glomerular filtration rate (eGFR), the percentage of patients achieving at least a 30% reduction in UACR, glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG), and serum creatinine (SCr).
(5) We also included safety outcomes such as hypoglycemia, dizziness, and all-cause mortality.

Data extraction

We extracted pertinent data from each eligible randomized controlled trial (RCT), which included:

(1) Study Characteristics: We documented the author's name, publication year, total number of randomized patients, follow-up duration, and trial registry identification number.
(2) Patient Demographics: Details such as age, diabetes duration, body mass index (BMI), baseline glycated hemoglobin (HbA1c) levels, and estimated glomerular filtration rate (eGFR) were recorded.
(3) Interventions: Specifics regarding the DPP-4 inhibitors administered and the control group regimen, including the generic names of drugs, were collected.

For any modifications to the initial intervention protocol, such as patients in the placebo group initiating DPP-4 inhibitors after 24 weeks, we ensured the collection of outcome data prior to this change. In cases where a trial was reported in multiple publications, we consolidated all findings into a single study representation. When trials were reported in both ClinicalTrials.gov and peer-reviewed literature, we conducted a meticulous comparison to ensure data consistency. For outcomes reported at various intervals, we prioritized data from the longest follow-up point for our analysis.

For the analysis of continuous variables, we obtained the average changes from baseline at the start of the study, along with their standard deviations, using these as indicative measures for both the DPP-4 inhibitor treatment group and the control group, which consisted of placebo or other blood glucose-lowering medications. For categorical variables, we collected the counts of participants experiencing each specific outcome.

Risk of bias assessment

To assess the potential for bias within the randomized controlled trials, we employed the evaluation tool developed by the Cochrane Collaboration. This tool evaluates various aspects, including the process of random sequence generation, the methods used to conceal allocation, the extent of blinding for participants and personnel, and the handling of outcome assessment for specific health events, such as heart failure or hospitalization due to heart failure, ensuring a thorough examination of the results' validity.

Data analysis

The focus of this meta-analysis was the variation in Urinary Albumin to Creatinine Ratio (UACR) from the beginning to the end of the study period. Additional outcomes of interest were alterations in Serum Creatinine (SCr), Fasting Plasma Glucose (FPG), Hemoglobin A1c (HbA1c), Fasting Blood Glucose (FBG), and Estimated Glomerular Filtration Rate (eGFR) over the same period. Safety was assessed by the occurrence of All-cause death, Dizziness, and Hypoglycemia. For continuous variables like HbA1c, we used the Standardized Mean Difference (SMD) with 95% Confidence Intervals (CIs) to measure differences, while for dichotomous variables such as incidence of hypoglycemia, we employed Odds Ratios (ORs) with 95% CIs. Where Standard Deviations (SDs) were not provided, we derived them from the standard error (SE) or the 95% CI. We also conducted subgroup analyses, focusing on eGFR and types of control interventions.

We assessed the variability among the study outcomes using the I^2 statistic, categorizing I^2 values above 60% as indicative of substantial heterogeneity. For our analysis, we employed the random effects model. Furthermore, we conducted subgroup and sensitivity analyses to investigate the underlying causes of this

heterogeneity. To detect reporting bias in the renal outcomes, we utilized funnel plots and Egger's test, applying these methods only when a sufficient number of studies were available for assessment.[16] All statistical analyses were carried out using Review Manager 5.4 software and STATA. For treatment effects, $P < 0.05$ was regarded as statistically significant, respectively.

Ethical approval

This article does not contain examinations performed on human participants in that ethical approval is not necessary.

Trial characteristics

Initially, our database search yielded 463 potential articles, to which we added 3 more from other sources, such as published meta-analyses and reviews. After removing 103 duplicates and screening out 314 irrelevant studies, we excluded an additional 26 studies due to various reasons, including their focus on animal trials, being cohort studies, lack of accessible data, or not involving patients with diabetic kidney disease (DKD). This process resulted in the selection of 23 articles that fulfilled our inclusion criteria, as depicted in the study selection flowchart in Figure 1.

Table 2S provides a comprehensive overview of the study characteristics. A total of 16,378 individuals were enrolled across the trials, with the number of participants per study ranging widely from 29 to 6,979. The duration of these studies varied significantly, with the shortest being 8 weeks and the longest spanning 302 weeks. In all of the randomized controlled trials (RCTs), participants continued on their pre-existing anti-diabetic treatments, which were primarily insulin regimens.

Regarding the baseline renal function as measured by Estimated Glomerular Filtration Rate (eGFR), 9 studies included patients with eGFR levels of 60 mL/min/1.73 m^2 or higher, while ten studies had a lower threshold of 30 mL/min/1.73 m^2. Notably, in 2 studies, the eGFR was reported to be below 30 mL/min/1.73 m^2. Furthermore, there were 2 instances where the baseline eGFR values were not explicitly defined in the study documentation. This variability in eGFR at study entry reflects the diverse patient populations and the spectrum of renal function considered in these clinical trials.

Assessment of study quality and risk of bias

The risk of bias for the included trials is presented in Supplementary Figure 1S. Among these articles, 2 were open-label studies,[17,18] which were considered to have a high risk of bias due to the blinding of participants and personnel.[19] Additionally, one study did not specify the method of subject allocation to groups, leading to an unclear risk of bias regarding random sequence generation[13].

Results

Efficacy outcomes

Changes in UACR and eGFR

Figure 2 illustrates the comparative changes in the urinary albumin-to-creatinine ratio (UACR) for patients treated with DPP-4 inhibitors versus control treatments. The meta-analysis revealed a statistically significant difference in UACR changes between the DPP-4 inhibitor group and the control group (SMD -0.23,95% CI: -0.41, -0.06; $p = 0.01$, I^2=76%).

Subgroup analysis using patients' eGFR revealed that among those with an eGFR $\leq$ 60 mL/min/1.73 m^2, DPP-4 treatments didn't significantly reduce UACR levels (SMD -0.06, 95% CI: -0.17, 0.05; $p = 0.25$, I^2=33%). However, for those with an eGFR above this threshold, DPP-4 inhibitors significantly decreased UACR levels (SMD -0.41, 95% CI: -0.72, -0.10; $p = 0.009$, $I^2 = 46\%$). Moreover, this disparity in UACR changes was statistically significant between the 2 subgroups ($p = 0.04$). Further subdivision based on control drug indicated that DPP-4 inhibitors significantly reduced UACR levels compared to placebo (SMD -0.30, 95% CI: -0.48, -0.13; $p = 0.0006$, $I^2 = 50\%$), yet displayed minimal effect compared to active drugs

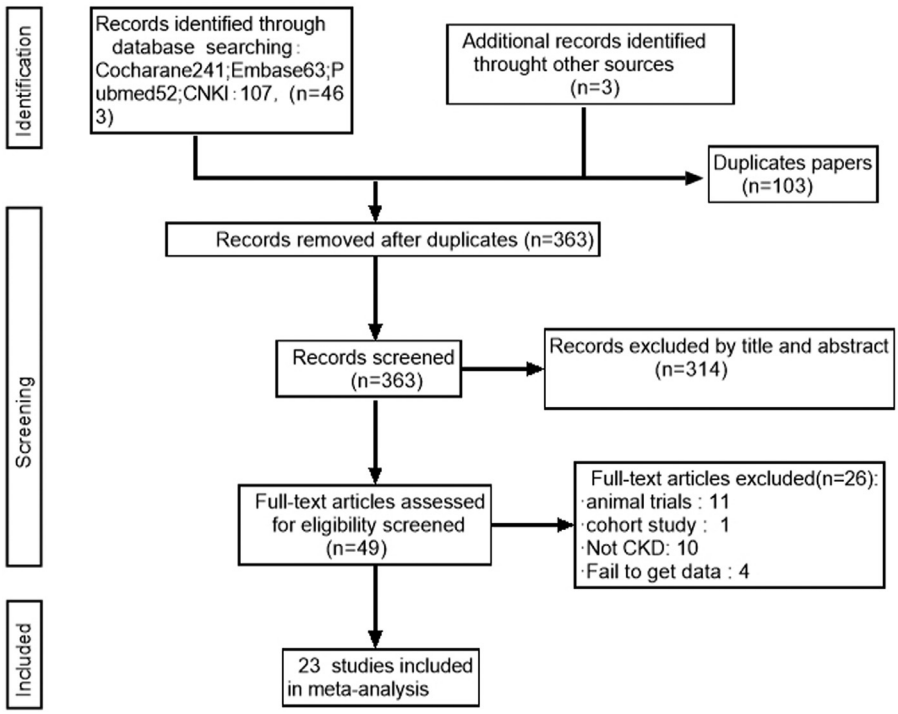

Figure 1. Flowchart of article selection.

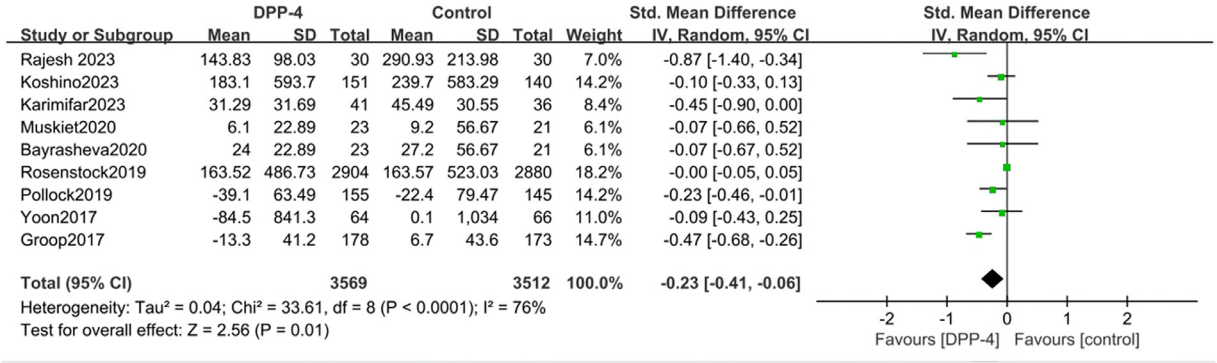

Figure 2. Standardized mean differences in changes in urine albumin-to-creatinine ratio (UACR) from baseline (mg/g) for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control drugs.

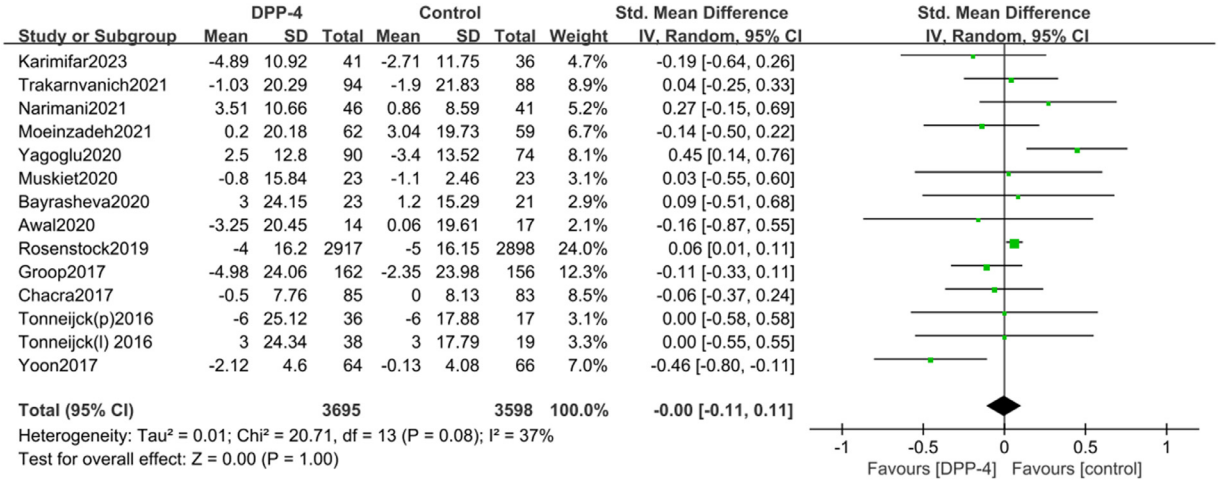

Figure 3. Standardized mean differences in changes in estimated glomerular filtration rate from baseline (mL/min/1.73 m^2) for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control drugs.

(SMD -0.00, 95% CI: -0.05, 0.05; $p = 0.81$, $I^2 = 0$ %) (Supplemental Figure 2S).

Figure 3 shows the comparison of changes in eGFR between DPP-4 inhibitors and controls. There were no significant differences between the groups in the overall analysis (SMD -0.00, 95% CI: -0.11, 0.11; $p = 1.00$, $I^2 = 37\%$). The funnel plot was asymmetrical, and Egger's test gave a *P* value of 0.345 (Supplemental Figure 3S). However, a subgroup analysis focusing on patients' eGFR revealed a significant increase in eGFR levels with DPP-4 inhibitors compared to active drugs (Supplemental Figure 9S), suggesting that certain patient populations may respond differently to DPP-4 inhibitors.

HbA1c

Figure 4 presents changes in HbA1c levels among DPP-4 inhibitors compared to controls. Overall changes in HbA1c were significantly different between groups (SMD -0.32, 95% CI: -0.51, -0.14; $P = 0.0006$, $I^2 = 85\%$). The test for heterogeneity demonstrated significant differences amongst studies ($p < 0.001$) which contributed to the asymmetrical appearance of the funnel plot (Supplemental Figure 4S), and Egger's test gave a *p* value of 0.089. Subgroup scrutiny using patients' eGFR and a class of control drugs keeps the same result as the overall analysis.

Fasting Blood Glucose (FBG)

Figure 5 depicts the comparative reduction in fasting blood glucose (FBG) levels between treatment groups receiving DPP-4 inhibitors and those in the control arm. Overall changes in FBG were significantly different between groups (SMD -0.18, 95% CI: -0.30, -0.05; $p = 0.005$, $I^2 = 67\%$). The assessment of heterogeneity across studies revealed significant variability ($p < 0.001$), indicating important differences in study outcomes. Furthermore, the symmetry observed in the funnel plot, along with a non-significant *P* value of 0.520 from Egger's test, suggests an absence of substantial publication bias (Supplemental Figure 5S).

Subgroup analysis using patients' eGFR revealed that among those with an eGFR > 60 mL/min/1.73 m^2, DPP-4 treatments didn't significantly reduce FBG levels (SMD -0.21, 95% CI: -0.54, 0.13; $p = 0.24$, $I^2 = 79\%$). However, for those with an eGFR ≤ 60, DPP-4 inhibitors significantly decreased FBG levels (SMD -0.18, 95% CI: -0.31, -0.05; $p = 0.006$, $I^2 = 55\%$). This disparity in FBG changes wasn't statistically significant between the 2 subgroups ($p = 0.89$). Another subgroup showed that compared to placebo, DPP-4 inhibitors significantly reduced FBG level. Different result was found that when compared to active drugs, DPP-4 inhibitors fail to reduce FBG level (Supplemental Figure 6S).

Serum creatinine (SCr)

Figure 6 showed a total of 4 studies assessed the change in SCr level, there was no significant difference in patient's SCr between DPP-4 inhibitors and the control group (SMD 0.15, 95% CI: -0.55, 0.86; $p = 0.67$, $I^2 = 90\%$). The test for heterogeneity was high across the studies ($p < 0.001$). The tests for funnel plot asymmetry were not performed on the SCr level because of the small number of studies.

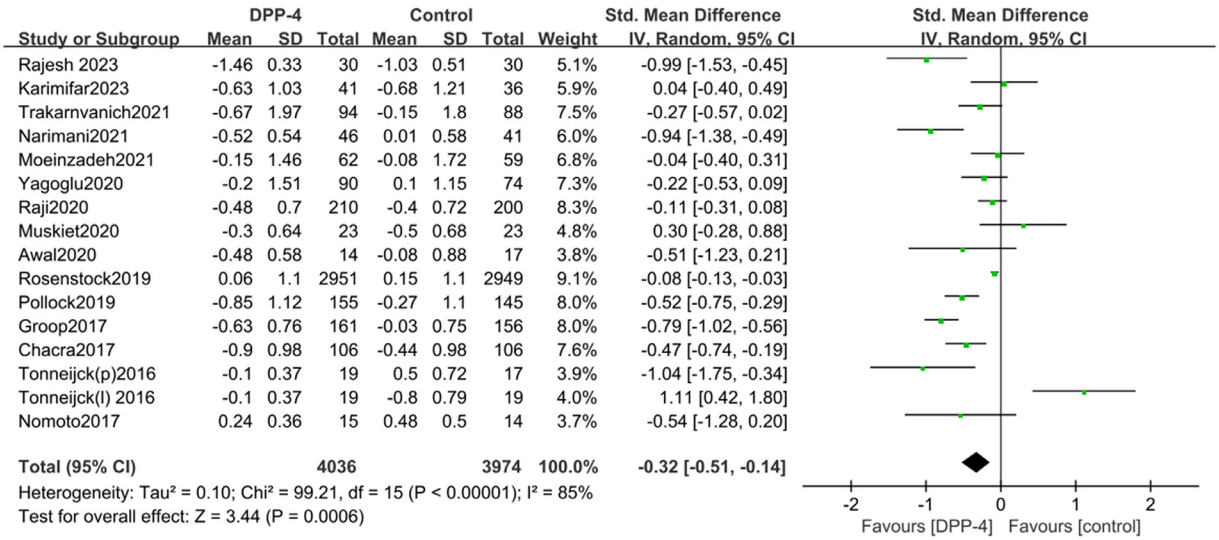

Figure 4. Standardized mean differences in changes in HbA1c (%) from baseline for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control group.

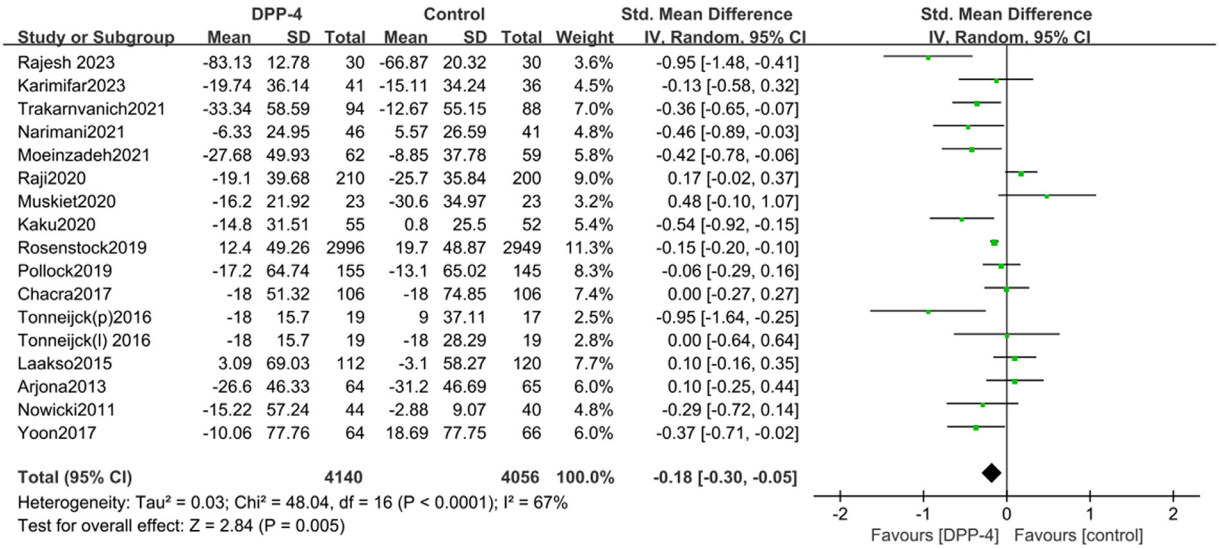

Figure 5. Standardized mean differences in changes in FBG (mg/dl) from baseline for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control group.

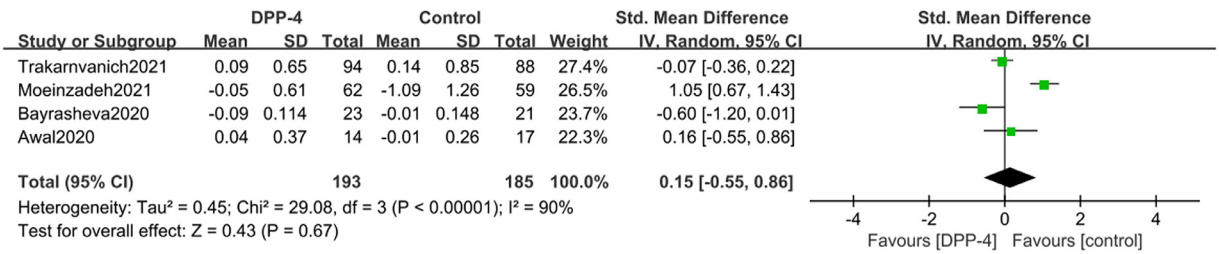

Figure 6. Standardized mean differences in changes in SCr (mg/dl) from baseline for dipeptidyl peptidase-4 (DPP-4) inhibitors versus the control group.

The percentage of patients achieving at least 30% reduction in UACR

Figure 7 shows a total of 4 studies assessed the percentage of patients achieving at least a 30% reduction in UACR, DPP-4 inhibitors were associated with significantly higher rates of the percentage of patients achieving at least 30% reduction in UACR compared with controls (OR = 1.73, 95% CI: 1.10, 2.73; $p = 0.02$, $I^2 = 79\%$). The test for heterogeneity was high across the studies ($p = 0.002$). The tests for funnel plot asymmetry were not performed in this field because of the small number of studies.

Safety outcome

All-cause death

Figure 8 shows 6 studies reported the incidence of all-cause death. Compared to the control group, DPP-4 inhibitors did not

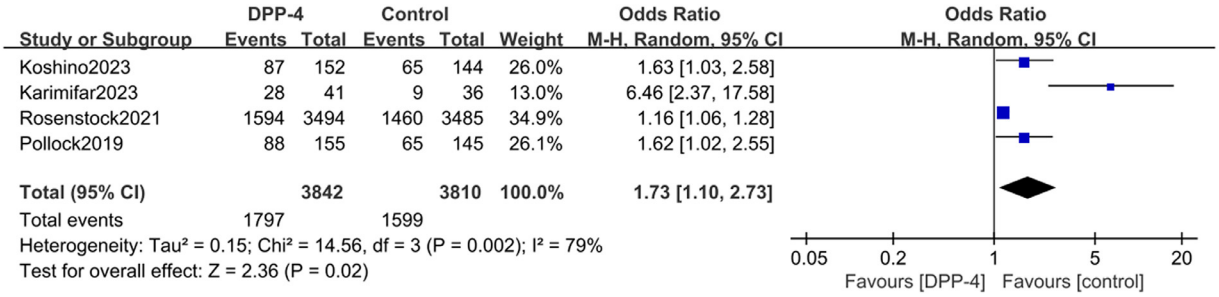

Figure 7. Odds Ratio of the percentage of patients achieving at least 30% reduction in UACR from baseline for dipeptidyl peptidase-4 (DPP-4) inhibitors versus the control group.

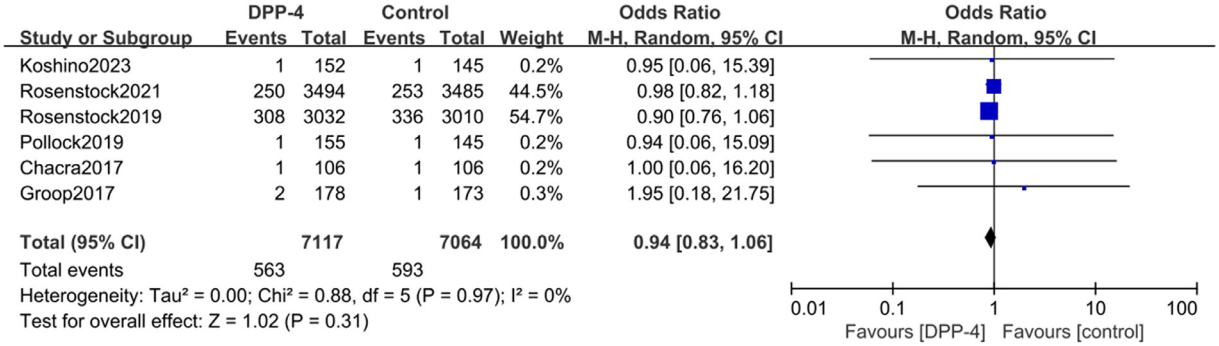

Figure 8. All-cause death for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control group.

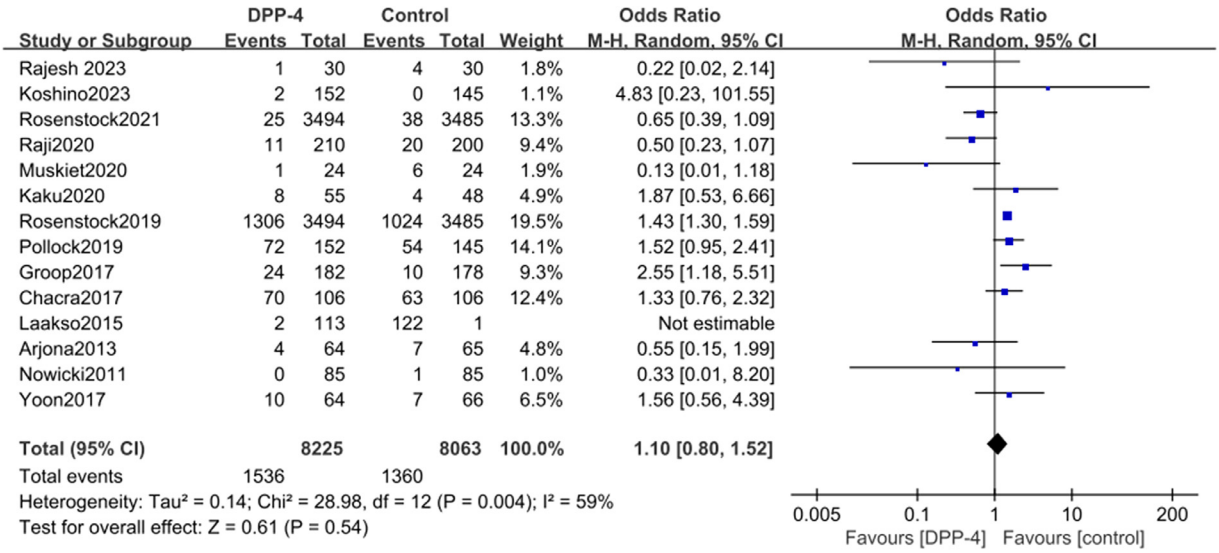

Figure 9. Hypoglycemia for dipeptidyl peptidase-4 (DPP-4) inhibitors versus control group.

increase the incidence of all-cause death (OR = 0.94, 95% CI: 0.83, 1.06; $p = 0.31$, $I^2 = 0\%$). Asymmetry in the funnel plot was not evaluated due to the small number of studies.

Hypoglycemia

An investigation involving 14 studies reported at least 1 event. The test for heterogeneity showed high across the studies ($I^2 = 59\%$, $p = 0.004$). The funnel plot was symmetrical, and Egger's test gave a P value of 0.701 (Supplemental Figure 7S). Figure 9 showed that compared to the control group, DPP-4 inhibitors did not increase the hypoglycemia events (OR = 1.10, 95% CI: 0.80, 1.52; $p = 0.54$).

Subgroup analysis using patients' eGFR revealed that among those with an eGFR $\leq$ 60 mL/min/1.73 m2, DPP-4 treatments significantly increased Hypoglycemia events (OR = 1.28, 95% CI: 1.01, 1.62; $p = 0.04$, $I^2 = 70\%$). However, for those with an eGFR above this threshold, DPP-4 inhibitors significantly decreased hypoglycemia events (OR = 0.41, 95% CI: 0.20, 0.81; $p = 0.01$, $I^2 = 0\%$). Moreover, this disparity in hypoglycemia events was statistically significant between the 2 subgroups ($p = 0.002$). Another subgroup based on patients' control drug demonstrated that compared with placebo, DPP-4 inhibitors significantly increased hypoglycemia events (OR = 1.54, 95% CI: 1.15, 2.07; $p = 0.004$, $I^2 = 0\%$). In comparison to active drugs, there were no significant differences between the 2 groups (OR = 0.70, 95% CI: 0.39, 1.27; $p = 0.24$, $I^2 = 49\%$) (Supplemental Figure 8S). This difference in

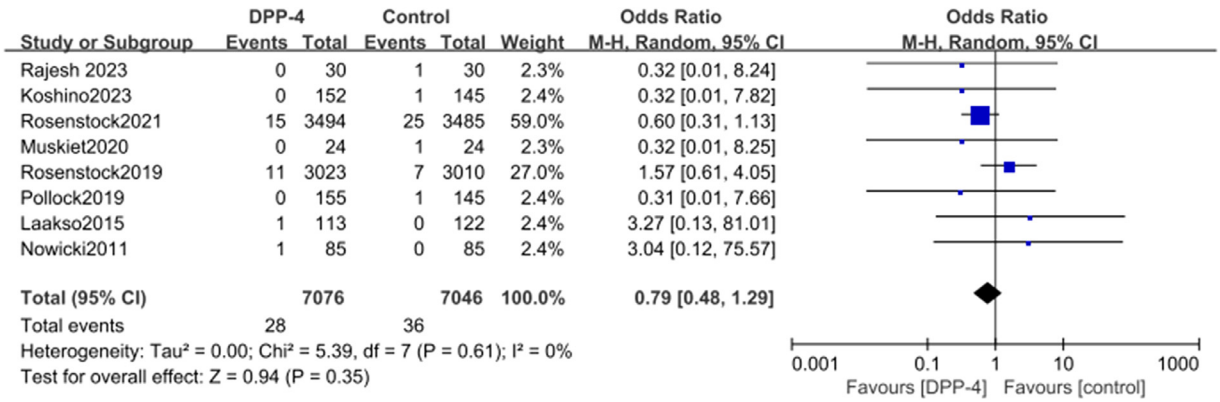

Figure 10. Dizziness for dipeptidyl peptidase-4 (DPP-4) inhibitors versus the control group.

hypoglycemia events was statistically significant between the 2 subgroups ($p = 0.02$).

Dizziness

Figure 10 shows 8 studies that reported the incidence of dizziness events. Compared to the control group, DPP-4 inhibitors did not increase the incidence of dizziness (OR = 0.79, 95% CI: 0.48, 1.29; $p = 0.35$, $I^2 = 0\%$). Asymmetry in the funnel plot was not evaluated due to the small number of studies.

Sensitivity analysis

Upon reviewing all endpoints, we evaluated how the main outcome was affected by the exclusion of each individual article. Results indicated no significant change in the pooled effect. Consequently, the stability of our findings was confirmed.

Discussion

Our findings indicate that DPP-4 inhibitors positively impacted key efficacy measures by lowering the urinary albumin to creatinine ratio (UACR), hemoglobin A1c (HbA1c), and fasting blood glucose (FBG) levels when compared to control medications. Additionally, a greater proportion of patients taking DPP-4 inhibitors achieved a significant 30% decrease in UACR. The safety profile of DPP-4 inhibitors was favorable, with no increased risk of all-cause mortality, dizziness, or hypoglycemia observed among the study population.

DPP-4 inhibitors showed positive effects in reducing UACR level, which was already found in previous studies.[20,21] Animal tests demonstrated that DPP-4 inhibitors protect the kidney by reducing tubulointerstitial renal fibrosis,[22] having a positive influence on renal functions in the DKD rat model.[23] Various pieces of evidence have shed light on the mechanisms through which DPP-4 inhibitors ameliorate albuminuria. Notably, early laboratory studies suggested that these inhibitors could mitigate diabetic kidney disease (DKD) by lessening oxidative stress, inflammation, and kidney tissue damage.[24-26] Moreover, the decrease in the breakdown of neuropeptide Y, due to DPP-4 inhibition, has been shown to intensify sympathetic activity and vasoconstriction through the Y1 receptor, particularly in patients on angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).[27] In our review, approximately 43.5% of the studies noted the use of ACEIs/ARBs as part of the background therapy, which may have interacted with the DPP-4 inhibitors to enhance their beneficial effects on the kidneys.

The efficacy of DPP-4 inhibitors in treatment varied depending on the comparator antidiabetic medication used in the control arm of the studies. While DPP-4 inhibitors demonstrated a notable decrease in urinary albumin to creatinine ratio (UACR) when pitted against placebo, their impact on UACR was less pronounced and essentially neutral when compared to active antidiabetic drugs such as Glimepiride. Moreover, it was discovered that when eGFR levels surpassed 60 mL/min/1.73 m^2, the DPP-4-using group significantly decreased UACR compared to the control, while for the subgroup with an eGFR below 60 mL/min/1.73 m^2, there wasn't a significant discrepancy between the 2 patient groups, despite the limitation stemming from a limited number of studies, the results indicate that DPP-4 inhibitors could be particularly beneficial for individuals with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or higher. Moreover, there was a marked increase in the proportion of patients who managed to achieve a reduction of at least 30% in the urinary albumin to creatinine ratio (UACR) while using DPP-4 inhibitors.

Upon eGFR comparison, there was no significant difference between DPP-4 inhibitors and the control group. Previous studies argued that DPP-4 inhibitors reduced eGFR in patients with diabetic albuminuria.[28,29] In contrast, Mori et al.[30] study showed that DPP-4 inhibitors reduce albuminuria using glycemic management and anti-inflammation effects without reducing eGFR. In subgroup analysis, our research found when compared with active drugs (2 research was Glimepiride,[31,32] one was liraglutide[33]), DPP-4 inhibitors significantly increased eGFR level, however, this effects were largely driven by the Glimepiride study.[32] Despite no demonstrable effect on eGFR or SCr, DPP-4 inhibitors showed a reduction in UACR, renal enhancement, and an anti-inflammatory response for DKD patients. Hence, additional comprehensive data are necessary to substantiate the significant clinical impact of DPP-4 inhibitors on renal outcomes.

Effective metabolic management aids prevention of CKD. Achieving a 0.9% HbA1c decrease from baseline results in a 24%–33% decline in diabetic nephropathy development.[34] Our investigation revealed that DPP-4 inhibitors effectively lowered hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) levels without a corresponding increase in hypoglycemic events in the overall analysis. This outcome is especially crucial for patients with chronic kidney disease, as there is a relative scarcity of glucose-lowering medications that have been extensively researched in this patient population.[35] An evaluation established by Ito et al.[36] noted no significant HbA1c difference between the linagliptin and control groups. Similar results emerged in another investigation where HbA1c levels did not significantly differ between the treatment and placebo groups.[37] However, Groop et al.'s[21] research demonstrated that linagliptin significantly enhanced glycemic control in DKD patients,

which is in line with our findings. Nonetheless, the impact of other variables such as participants' dietary adherence and physical activity must not be disregarded, as these may influence plasma glucose control.

As for safety outcomes, no significant difference was observed between the 2 groups in the overall analysis; however, a subgroup analysis based on the type of control drugs suggested that DPP-4 inhibitors significantly increased the risk of hypoglycemia compared to placebo. Prior studies corroborated similar findings relating to an increased risk of hypoglycemia with DPP-4 inhibitors for diabetes patients.[38–41] Specifically, our subjects' mean age was 63.3, and one recent research demonstrates that DPP-4 inhibitors significantly increase hypoglycemia risk among diabetes patients aged over 60.[42] Further study is required to ascertain the safety of DPP-4 inhibitors, particularly in elderly patients.

In our analysis, while DPP-4 inhibitors did not show an overall increased risk of hypoglycemic events, it is important to note that a subgroup analysis based on the type of control drugs revealed a significant increase in the risk of hypoglycemia compared to placebo. This finding underscores the importance of considering the specific characteristics of the patient population and the type of comparator when evaluating the safety profile of DPP-4 inhibitors. The observed increase in hypoglycemia risk in the subgroup analysis may be attributed to differences in the pharmacological properties of the control drugs, patient demographics, or other confounding factors that were not controlled for in the overall analysis. Therefore, while DPP-4 inhibitors appear to be safe in the general population, caution should be exercised, especially when considering their use in elderly patients or in settings where the control drug may predispose to hypoglycemia.

Strengths and limitations

This is the first endeavor to assess the safety and efficacy of DPP-4 inhibitors in individuals with DKD patients. This meta-analysis boasts its strength in incorporating all newly released trials up to January 2024. A considerable number of participants was involved, and preplanned analyses were conducted alongside double data abstraction verification and maintaining superior trial quality. This strategic approach significantly diminishes potential biases.

There are several limitations in the present study. First, the number of studies included in the analysis of the percentage of patients achieving at least a 30% reduction in UACR or SCr is relatively small. Second, the test of heterogeneity for several results showed substantial heterogeneity across the studies. Third, the current meta-analysis encompasses trials with varying durations, spanning between 8 and 302 weeks. It is conceivable that such variations in study length could potentially influence the findings related to the specific outcome variables under examination. Thus, the results of our meta-analysis should be interpreted cautiously.

Conclusion

This meta-analysis demonstrates that DPP-4 inhibitors confer renoprotection in patients with diabetic kidney disease (DKD). The observed significant reductions in urinary albumin-to-creatinine ratio (UACR) and glycated hemoglobin (HbA1c) levels suggest an improvement in renal function and glycemic control, respectively. Moreover, the absence of an increased risk of hypoglycemia with DPP-4 inhibitor use further enhances their safety profile. These findings collectively support the use of DPP-4 inhibitors as a treatment option for DKD, particularly in patients seeking to maintain renal function and blood glucose control without the risk of hypoglycemia.

Declaration of competing interest

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Acknowledgments

Adili Tuersun: Writing—original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Munire Mohetaer:** Munire has provided invaluable insights, particularly during the revision process, and has been instrumental in enhancing the quality and depth of our study. **Guan Xin Hou:** Writing—review and editing, Formal analysis. **Gang Cheng:** Writing—review and editing, Validation, Supervision, Formal analysis, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2024.100763.

References

1. Sandoval D A, D'alessio D A. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. *Physiol Rev*. 2015;95(2):513–548.
2. Thomas M C, Cooper M E, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nature Rev Nephrol*. 2016;12(2):73–81.
3. Thomas M C, Brownlee M, Susztak K, et al. Diabetic kidney disease. *Nature Rev Dis Primers*. 2015;1:15018.
4. Niu J, Zhang X, Li M, et al. Risk of cardiovascular disease, death, and renal progression in diabetes according to albuminuria and estimated glomerular filtration rate. *Diabetes Metab*. 2023;49(2):101420.
5. Reidy K, Kang H M, Hostetter T, et al. Molecular mechanisms of diabetic kidney disease. *J Clin Invest*. 2014;124(6):2333–2340.
6. Cardoso C R L, Leite N C, Moram C B M, et al. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. 2018;17(1):33.
7. Shubrook J H, Neumiller J J, Wright E. Management of chronic kidney disease in type 2 diabetes: screening, diagnosis and treatment goals, and recommendations. *Postgrad Med*. 2022;134(4):376–387.
8. Mulvihill E E, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. *Endocr Rev*. 2014;35(6):992–1019.
9. Scheen A J. Efficacy /safety balance of DPP-4 inhibitors versus SGLT2 inhibitors in elderly patients with type 2 diabetes. *Diabetes Metab*. 2021;47(6):101275.
10. Bae J H, Kim S, Park E G, et al. Effects of dipeptidyl peptidase-4 inhibitors on renal outcomes in patients with type 2 diabetes: a systematic review and meta–analysis. *Endocrinol Metab (Seoul)*. 2019;34(1):80–92.
11. Mosenzon O, Leibowitz G, Bhatt D L, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. *Diabetes Care*. 2017;40(1):69–76.
12. Cornel J H, Bakris G L, Stevens S R, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. *Diabetes Care*. 2016;39(12):2304–2310.
13. Rajesh K, Rajeshware M R M, Asuvathi R. Randomized and comparative study analyzing efficacy and safety profile of sitagliptin in early diabetic nephropathy. *Natl J Physiol Pharm Pharmacol*. 2023;13(9):1933–1937.
14. Karimifar M, Afsar J, Amini M, et al. The effect of linagliptin on microalbuminuria in patients with diabetic nephropathy: a randomized, double blinded clinical trial. *Sci Rep*. 2023;13(1):3479.
15. Page M J, Mckenzie J E, Bossuyt P M, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clin Res ed)*. 2021;372:n71.
16. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2018;74(3):785–794.
17. Nomoto H, Miyoshi H, Sugawara H, et al. A randomized controlled trial comparing the effects of dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin. *Diabetol Metab Syndr*. 2017;9(1):2.
18. Trakarnvanich T, Satirapoj B, Suraamornkul S, et al. Effect of Dipeptidyl Peptidase-4 (DPP-4) Inhibition on Biomarkers of Kidney Injury and Vascular Calcification in Diabetic Kidney Disease: A Randomized Controlled Trial. *J Diabetes Res*. 2021:2021.
19. Li C, Luo J, Jiang M, et al. The Efficacy and Safety of the Combination therapy with GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis. *Front Pharmacol*. 2022;13:838277.
20. Cooper M E, Perkovic V, Mcgill J B, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of

the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. *Am J Kidney Dis*. 2015;66(3):441–449.
21. Groop P H, Cooper M E, Perkovic V, et al. Linagliptin and its effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: the randomized MARLINA-T2D trial. *Diabetes Obes Metab*. 2017;19(11):1610–1619.
22. Ren X, Zhu R, Liu G, et al. Effect of sitagliptin on tubulointerstitial Wnt/β-catenin signalling in diabetic nephropathy. *Nephrology (Carlton)*. 2019;24(11):1189–1197.
23. Mohamed R H, Sedky A A, Hamam G G, et al. Sitagliptin's renoprotective effect in a diabetic nephropathy model in rats: the potential role of PI3K/AKT pathway. *Fundam Clin Pharmacol*. 2022;36(2):324–337.
24. Jung G S, Jeon J H, Choe M S, et al. Renoprotective effect of gemigliptin, a dipeptidyl peptidase-4 inhibitor, in streptozotocin-induced type 1 diabetic mice. *Diabetes Metab J*. 2016;40(3):211–221.
25. Sharkovska Y, Reichetzeder C, Alter M, et al. Blood pressure and glucose independent renoprotective effects of dipeptidyl peptidase-4 inhibition in a mouse model of type-2 diabetic nephropathy. *J Hypertens*. 2014;32(11):2211–2223 discussion 23.
26. Wu M Z, Chandramouli C, Wong P F, et al. Risk of sepsis and pneumonia in patients initiated on SGLT2 inhibitors and DPP-4 inhibitors. *Diabetes Metab*. 2022;48(6):101367.
27. Hubers S A, Wilson J R, Yu C, et al. DPP (Dipeptidyl Peptidase)-4 inhibition potentiates the vasoconstrictor response to NPY (Neuropeptide Y) in humans during renin-angiotensin-aldosterone system inhibition. *Hypertension*. 2018;72(3):712–719.
28. Narimani R, Kachuei A, Rezvanian H, et al. Effect of sitagliptin on proteinuria in patients with type 2 diabetes-A renoprotective effect of sitagliptin. *J Res Med Sci*. 2021;26(1):35.
29. Yoon S A, Han B G, Kim S G, et al. Efficacy, safety and albuminuria-reducing effect of gemigliptin in Korean type 2 diabetes patients with moderate to severe renal impairment: A 12week, double-blind randomized study (the GUARD Study). *Diabetes, Obesity Metab*. 2017;19(4):590–598.
30. Mori H, Okada Y, Arao T, et al. Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2014;5(3):313–319.
31. Muskiet M H A, Tonneijck L, Smits M M, et al. Effects of DPP-4 inhibitor linagliptin versus sulfonylurea glimepiride as add-on to metformin on renal physiology in overweight patients with type 2 diabetes (RENALIS): a randomized, double-blind trial. *Diabetes Care*. 2020;43(11):2889–2893.
32. Rosenstock J, Perkovic V, Johansen O E, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69–79.
33. Tonneijck L, Smits M M, Muskiet M H, et al. Renal effects of DPP-4 inhibitor sitagliptin or GLP-1 receptor agonist liraglutide in overweight patients with type 2 diabetes: a 12-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2016;39(11):2042–2050.
34. Kirkman M S, Mahmud H, Korytkowski M T. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes mellitus. *Endocrinol Metab Clin North Am*. 2018;47(1):81–96.
35. Lo C, Toyama T, Wang Y, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev*. 2018;9(9):Cd011798.
36. Ito H, Abe M, Antoku S, et al. Comparison of the antidiabetic effects of linagliptin among groups with a normal renal function and a mild or severe renal impairment - retrospective observation study of Japanese patients with type 2 diabetes mellitus. *Expert Opin Pharmacother*. 2015;16(3):289–296.
37. Moeinzadeh F, Iraj B, Mortazavi M, et al. The renoprotective effect of linagliptin in type 2 diabetic patients with severely increased albuminuria. *Iran J Kidney Dis*. 2021;15(5):344–350.
38. Cooper M E, Rosenstock J, Kadowaki T, et al. Cardiovascular and kidney outcomes of linagliptin treatment in older people with type 2 diabetes and established cardiovascular disease and/or kidney disease: a prespecified subgroup analysis of the randomized, placebo-controlled CARMELINA® trial. *Diabetes Obes Metab*. 2020;22(7):1062–1073.
39. Kadowaki T, Kondo K. Efficacy and safety of teneligliptin added to glimepiride in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study with an open-label, long-term extension. *Diabetes Obes Metab*. 2014;16(5):418–425.
40. Ledesma G, Umpierrez G E, Morley J E, et al. Efficacy and safety of linagliptin to improve glucose control in older people with type 2 diabetes on stable insulin therapy: a randomized trial. *Diabetes Obes Metab*. 2019;21(11):2465–2473.
41. Leiter L A, Teoh H, Braunwald E, et al. Efficacy and safety of saxagliptin in older participants in the SAVOR-TIMI 53 trial. *Diabetes Care*. 2015;38(6):1145–1153.
42. Doni K, Bühn S, Weise A, et al. Safety of dipeptidyl peptidase-4 inhibitors in older adults with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Ther Adv Drug Saf*. 2022;13:20420986211072383.