ORIGINAL ARTICLE

Effect of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcome in Diabetes Mellitus: A Systematic Review and Meta-analysis

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Abstract

Diabetic nephropathy is a common microvascular consequence, described by a persistent rise in albuminuria or a considerable fall in the predictable estimated glomerular filtration rate (eGFR). Dipeptidyl peptidase-4 (DPP-4) inhibitors are frequently utilized to treat diabetes mellitus (DM), although it's unclear how significant these drugs are in terms of specific renal outcomes (RO). This study aims to determine the impact of DPP-4 inhibitors (DPP4-I) on renal consequences in individuals with DM. The relevant studies were searched in PubMed, Google Scholar, and SciHub, and then filtered concurring to the exclusion and inclusion criteria. The preferred reporting item for systematic reviews and meta-analysis criteria were adhered to, and the extracted data were evaluated using the RevMan software. A 95% confidence interval (CI) was calculated in addition to the overall estimate measure. I-squared (I^2) statistics were used to assess the studies' heterogeneity. The qualitative evaluations of publication bias were done using the funnel plot. Ten randomized controlled studies with a total of 39,124 people were eligible for the investigation. At 24 weeks, eGFR in DM patients was not substantially affected by the DPP4-I (mean differences [MD] 4.31; 95% CI −4.93, 13.54; $P < 0.00001$, heterogeneity $I^2 = 95\%$; $P = 0.36$). Further at 52 weeks also, the changes in eGFR were found non-significant (MD 0.24 [−1.68, 2.16]) as compared to the control group (CG). The changes in urine albumin-creatinine ratio were also found non-significant as compared to the CG. The adverse events in the DPP4-I groups were also found non-significant as compared to the CG which indicates the safety of DPP4-I. Overall, more randomized clinical trials are required to confirm the exact role of DPP4-I on RO in DM.

Key words: Diabetes mellitus, dipeptidyl peptidase-4 inhibitor, estimated glomerular filtration rate, kidney failure, meta-analysis, systematic review

INTRODUCTION

One of the most serious health issues associated with non-communicable diseases worldwide is diabetes mellitus (DM). The condition has become more common over the past few decades, and scientists are attempting to treat it globally. One of the microvascular complications of DM is diabetic kidney disease (DKD). About one-third of renal replacement treatment patients have DKD.[1] In the past 10 years, many innovative treatments for DM have become accessible. Thus, two prominent examples of incretin-based therapies that have essentially allowed for

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an evolution in approach from focusing solely on slashing blood glucose levels to stratagems that target the fundamental pathophysiological mechanisms are glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 inhibitors (DPP4-I).[2,3] The 2006 saw the introduction of a novel family of anti-diabetic drugs called DPP4-I, sometimes known as lipitins. They work by preventing the breakdown of two incretin hormones (GLP-1) and glucose-dependent insulinotropic polypeptide. As a result, while glucagon secretion falls, post-prandial glucose-dependent insulin secretion rises. GLP-1 agonists have outperformed DPP4-I indirect comparisons; nevertheless, glinides are much less effective anti-diabetic drugs and there is insufficient data to compare them to DPP4-I. Beyond the lower renal risk provided by glycemic management, non-clinical research has shown the pleiotropic impact of DPP4-I on the kidney, and some clinical evidence shows a likely nephroprotective drift.[4,5] Although DPP4-I has been used with chronic kidney disease (CKD) and in older individuals, it is still unclear how independently these conditions could affect renal results. The implementation of strict regulations by regulatory bodies has encouraged extensive clinical trials evaluating the cardiovascular safety of new glucose-lowering drugs.[6,7]

A small number of these trials examining cardiovascular outcomes have also suggested that using DPP4-I may have drug-specific renoprotective benefits; however, other assessments have produced uneven findings on renal outcomes (RO).[8] In some seminal trials, the RO were secondary or supplementary objectives.[8] Furthermore, it is difficult to conclude that the possible renoprotection applies to everyone because a large number of these trials were mostly carried out in patients who had a known cardiovascular disease or were at high risk for developing one.[9,10] Although this is controversial, recent evidence indicates that DPP4-I may offer renoprotection effects independent of those brought about by glycemic control in DM individuals. To tackle this issue, we carried out the tiled study. Using DPP4-I as a comparison to placebo or other antidiabetic drugs (non-DPP4-I), we looked into how the drug affected RO.

METHODS

Study design

The preferred reporting item for systematic reviews and meta-analysis (PRISMA) statements was employed to design this study.[11] We looked through PubMed, Google Scholar, and SciHub for articles that were published before August 2024. The MeSH terms along with Boolean operators were used to search the relevant studies. The complete search strategy has been mentioned in the supplementary file.

Study selection

Two authors (MI and SSA) independently searched these electronic databases for the data collection. Only randomized controlled trial (RCTs), or randomized controlled trials, were used to study the impact of DPP4-I on estimated glomerular filtration rate (eGFR). The following criteria were established for inclusion: (i) DPP4-Iimpact on eGFR was examined and urine albumin-creatinine ratio (UACR) as primary outcome measures; (ii) baseline and follow-up data on renal parameters change was detected and documented; and (iii) type 2 DM (T2DM) was diagnosed in the patients; (iv) reported all type of side effects; and (v) randomized controlled clinical trials. However, the following were the exclusion criteria: (i) research not involving humans; (ii) no documentation of eGFR; (iii) abstracts, reviews, conference papers and meetings; and (iv) trials where the complete text has been published in languages other than English.

Data extraction

The data were extracted independently by the two authors using pre-validated data extraction forms. Mean changes from baseline with standard deviations were extracted for continuous variables related to our defined key RO of interest, which include UACR and eGFR variations, in both the DPP4-I intervention group and the non-DPP4-I control group (CG). The research aims to determine the following: baseline UACR and eGFR, background therapy for glycemic management, number of randomly assigned participants, length of trial, intervention and comparator arms, and history of heart failure, CKD, and cardiovascular disease (eGFR). To examine all pertinent extracted data, review manager 5 was employed. The risk of bias valuation was also assessed by the authors independently.

Quality assessment

The modified grading system (Jadad scale) was utilized by the authors to measure the procedural quality of the encompassed investigations.[12] A review of the proper conduct of randomization, treatment allocation concealment, baseline group similarity, clinician blinding, and withdrawal and dropout descriptions were among the topics covered in this. The methodological quality of each study was graded, with 0 representing the lowest quality and 8 representing the most.

Statistical analysis

The effect size of UACR for pre-determined timeframes (24 weeks) and eGFR (24/52 weeks) was assessed by computing mean differences (MD) with 95% confidence intervals (CI). The impact size for the incidence of side events or all-cause mortality during 52 weeks and until the study's end was assessed using relative risks (RR) with 95% CIs. The selection of model was done based on the variations among the included studies. The random effect model was preferred over fixed effect model if variations among the

included studies was high whereas fixed effect model was preferred if variation among included studies was less. Using the fixed effects model, we combined the impact size (MD or RR) from all pertinent included research. We investigated the random effects model in cases with significant statistical heterogeneity. To measure statistical heterogeneity, I^2 statistics and the χ^2 test were employed. $P = 50\%$ were considered significant for statistical heterogeneity. All the analysis was done using review manager 5.

RESULTS

Search and study qualities

A total of 230 articles were identified initially, and then after applying filters, 95 studies were screened centered on title and abstracts. Only, ten of these articles fulfilled the qualifying requirements and were incorporated into the meta-analysis.[13-21] All of the screening strategies are represented by the PRISMA flowchart in Figure 1. A total of 39,124 patients in all were enrolled in the trial and there were between 48 (minimum) and 16492 (maximum) persons participating in these investigations. A summary of the research features for the chosen studies is specified in Table 1.

Quality assessment

The RCTs were evaluated using the Jaded scale, and all nineteen of the studies were deemed outstanding. Each RCT's methodological quality was given a score between 0 and 8, where 0 denoted the lowest quality and 8 the greatest. Table 1 shows that most RCTs had well-designed designs and had high-quality rating scores ranging from 3 to 7.

Changes in eGFR

The study's 24-week results encompassed 356 patients; the DPP4-Iand CG did not exhibit a distinct rate of change in eGFR, and the evidence quality was deemed inadequate (MD 4.31; 95% CI −4.93, 13.54; $P < 0.00001$, Heterogeneity $I^2 = 95\%$; $P = 0.36$) [Figure 2]. The detected effects (MD: 0.24; 95% CI 0.24, 2.16; $P < 0.00001$, Heterogeneity $I^2 = 97\%$; $P = 0.81$) [Figure 3] at 52 weeks with 16,863 patients included in the research were comparable to those at previous periods, although the evidence quality was incredibly little.[13,15,20,21] Because of the results' indirectness, inconsistency, and imprecision, the evidence quality supporting this result at various times in time has to be reduced.

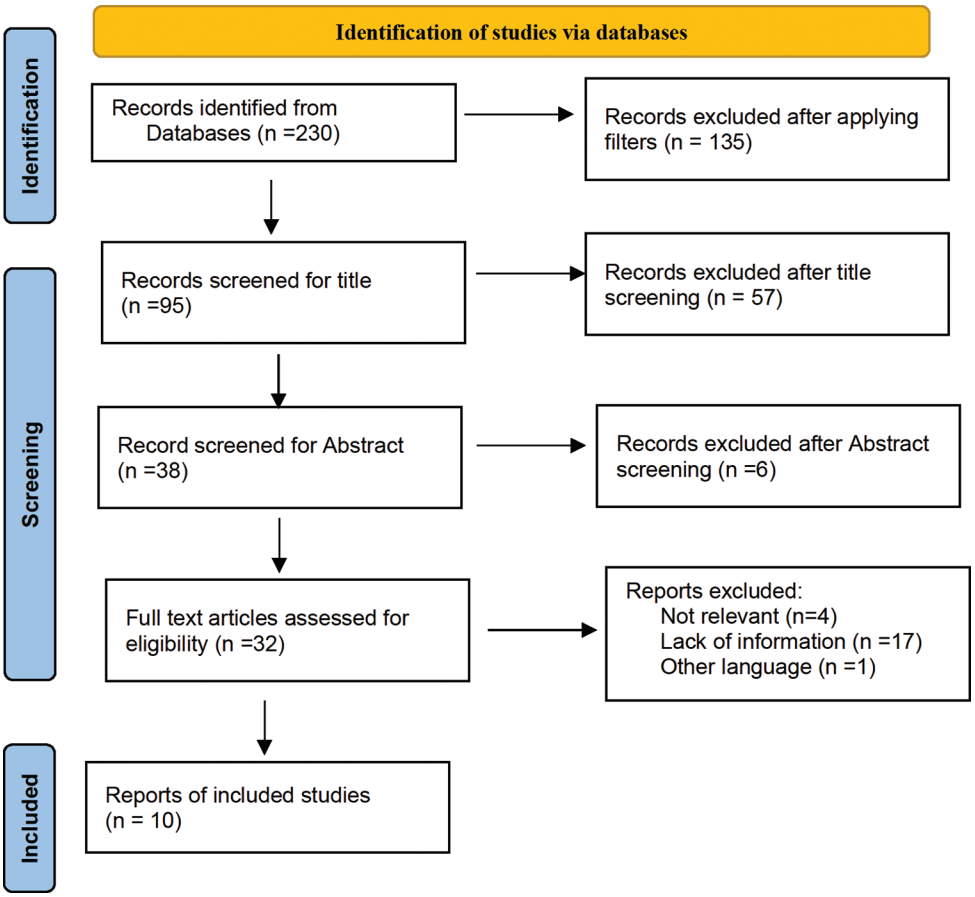

Figure 1: The preferred reporting item for systematic reviews and meta-analysis chart

Table 1: Characteristics of included studies

S. No.	Author	Year	Place	Total sample size	Age (year)	Experimental sample size	Experimental (dose)	Control sample size	Control (dose)	Study duration
1	Cornel[13]	2016	Multicenter	14671	65.9±9.4	7332	100 mg–25 mg Sitagliptin	7339	Placebo	3 years
2	Groop[14]	2017	Multicenter	360	61.0±10.0	182	5 mg linagliptin	178	Placebo	24 W
3	McGill[15]	2013	USA	133	64.9±9.1	68	5 mg linagliptin	65	Placebo	52 W
4	Chacra[16]	2017	Multicenter	213	65.9±9.4	107	25–12.5 mg once in a week omarigliptin	106	Placebo	24 W
5	Mosenzon[17]	2017	Multicenter	16492	65±9.0	8280	2.5–5 mg OD saxagliptin	8212	Placebo	2.1 years
6	Rosenstock[18]	2019	Multicenter	6991	65.9±9.1	3499	5 mg linagliptin	3492	Placebo	1.7 years
7	Tanaka[19]	2017	Japan	48	64.7±10.1	25	25 mg alogliptin	23	Vildagliptin	24 W
8	Tanaka[19]	2017	Japan	132	66.4±10.2	64	25 mg alogliptin	68	Vildagliptin	24 W
9	Hsu[20]	2022	Taiwan	2202	63.18±11.18	1101	NR	1101	NR	5 years
10	Narimani[21]	2021	Iran	84	58.47±7.33	43	50 mg sitagliptin	41	Placebo	12 W

S. No.	Author	Year	Place	Follow-up	Outcomes reported	Baseline eGFR	Treatment naïve (N)/ experienced (E)	Background treatment	Co-morbidities	Quality assessment
1	Cornel[13]	2016	Multicenter	52 W	All-cause mortality; AE; UACR; eGFR	>30	E	Insulin; sulfonylurea; pioglitazone; metformin	Dyslipidemia; myocardial infarction; heart failure; peripheral arterial disease; cerebrovascular disease; coronary artery disease	7
2	Groop[14]	2017	Multicenter	24 W	AE; UACR; eGFR	>30	N	NA	Hypertension; Obesity	7
3	McGill[15]	2013	USA	12 W; 52 W	AE; eGFR	>30	E	Alpha-glucosidase inhibitors; pioglitazone; meglitinides; sulfonylurea; insulin	Metabolic syndrome; diabetic retinopathy; diabetic nephropathy; hypertension	6
4	Chacra[16]	2017	Multicenter	24 W	AE; eGFR	>60	N and E	Oral hypoglycemics; Insulin	Obesity	7
5	Mosenzon[17]	2017	Multicenter	52 W, EOT	All-cause mortality; AE; UACR; eGFR	≤50	N and E	Insulin; thiazolidinediones; sulfonylureas; metformin	Hyperlipidemia; hypertension; heart failure; established CVD	7
6	Rosenstock[18]	2019	Multicenter	12 W; 52 W; EOT	All-cause mortality; AE; UACR; eGFR	≥15	E	Sulfonylurea; metformin; insulin	Obesity; Chronic kidney disease; atrial fibrillation; heart failure; ischemic heart disease; hypertension	7

(Contd...)

Table 1: *(Continued)*

S. No.	Author	Year	Place	Total sample size	Age (year)	Experimental sample size	Experimental (dose)	Control sample size	Control (dose)	Study duration
7	Tanaka[19]	2017	Japan	12 W; 24 W	AE; UACR; eGFR	≥ 60	N and E	Alpha-glucosidase inhibitors; pioglitazone; metformin; sulfonylurea		6
8	Tanaka[19]	2017	Japan	12 W; 24 W	AE; UACR; Egfr	≥60	N	Alpha-glucosidase inhibitors; pioglitazone; sulfonylurea; sulfonylurea		6
9	Hsu[20]	2022	Taiwan	1 year	AE; eGFR	>30	N	Anti-gout drugs; antihypertensives; statins; ARBs; ACEIs; direct renin inhibitors	Obesity; gout; hypertension; hyperlipidemia; cerebrovascular disease; heart failure; coronary artery disease	3
10	Narimani[21]	2021	Iran	12 W	ACR; eGFR	NR	N	NR	NR	4

eGFR: Estimated glomerular filtration rate, UACR: Urine albumin-creatinine ratio, W=Weeks; Yr=years

Changes in UACR

However, during 24 weeks of treatment, vildagliptin and alogliptin did not vary in terms of UACR change [Figure 4; $n = 180$; 95% CI 7.68–46.58; MD: 19.45; 2 trials; $n = 180$]. Because of the inconsistent and imprecise results, the evidence's quality was low. One trial's active run-in phase may have contributed to heterogeneity.

Adverse events

Figure 5 shows the extensive data on adverse events that were gathered from 10 individuals, totaling 880. Of the 445 DPP4-I users, 168 experienced adverse events, and of the 435 non- DPP4-I users, 174 were noted. The two groups' adverse events did not vary meaningfully ($P = 0.33$; RR 0.93 [95% CI, 0.80, 1.08]; Heterogeneity $I^2 = 0\%$; $P < 0.93$). Most of the negative effects were transient and didn't need to be addressed.

DISCUSSION

A thorough review and meta-analysis found that DPP4-I improved RO in patients with T2DM by lessening albuminuria when likened to a placebo/other medication. Medication with a DPP4-I caused a modest drop in eGFR in comparison to controls. Every group shared a similar risk of end-stage renal disease (ESRD). DPP4-I successfully lower the chance of microalbuminuria and macroalbuminuria starting and worsening. These favorable results were mostly impelled by the SAVOR-TIMI 53 study.[22] Nevertheless, our meta-analysis's findings that DPP4-I lower albuminuria was supported by drops in UACR detected in other clinical studies.[23] Research indicates that DPP4-I may help albuminuria through a variety of methods. DPP4-I have been revealed in pre-clinical investigations to ameliorate DKD by lessening inflammation, oxidative stress, and histologic alterations in renal damage.[24]

Without affecting blood glucose levels, linagliptin inhibited the endothelial-to-mesenchymal change and restored microRNA 29s, which reduced kidney fibrosis in streptozotocin-induced diabetic rats.[25] DPP4-I raise stromal cell-derived factor-1α levels, which have antifibrotic and antioxidative characteristics.[24] Furthermore, using DPP4-I inhibitors caused natriuresis in T2DM individuals.[24,25] They mostly affected the distal renal tubule, but they did not have the same natriuretic effects on the proximal tubule similar to the SGLT2 inhibitors (SGLT2I).[26] Moreover, diabetic mice had a diminished natriuretic response to DPP4-I.

Through their antifibrotic, anti-inflammatory, and antioxidant properties, DPP4-I may lower albuminuria without changing renal hemodynamics. Remarkably, the type of antidiabetic medication used in the CG affected the direction of the

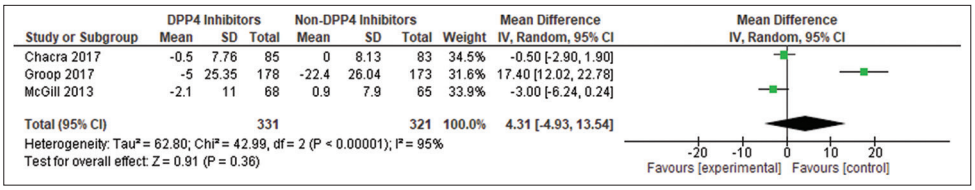

Figure 2: Changes in estimated glomerular filtration rate after 24 weeks

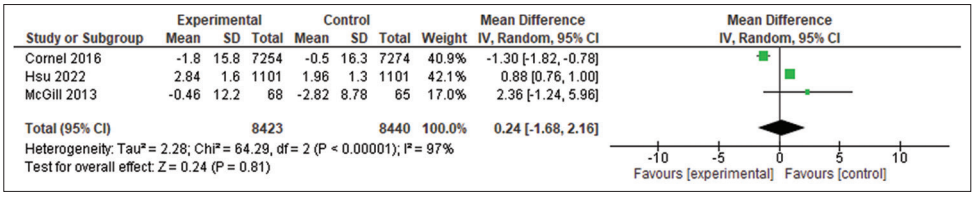

Figure 3: Changes in estimated glomerular filtration rate after 52 weeks

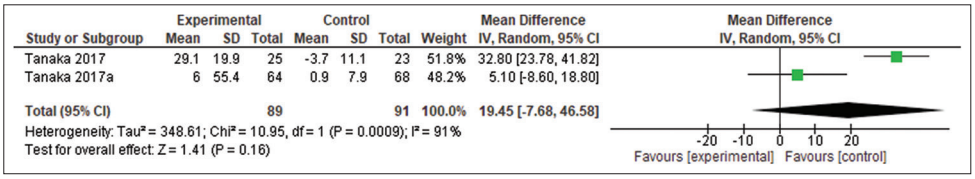

Figure 4: Changes in urine albumin-creatinine ratio after 24 weeks

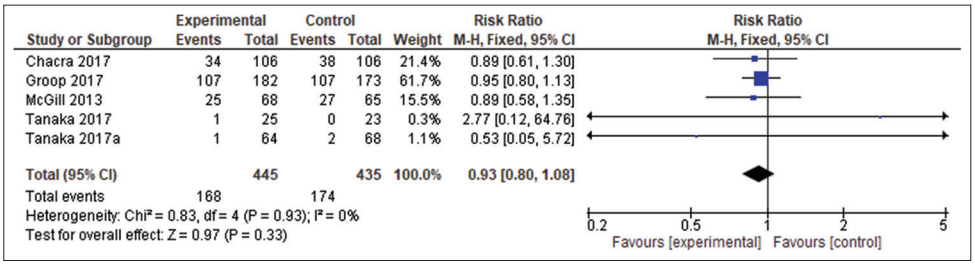

Figure 5: dipeptidyl peptidase-4 (DDP-4) versus non-DDP-4-I: A forest plot of unfavourable events

DPP4-I therapeutic effects. When compared to both SGLT2I and controls, DPP4-I raised UACR, but not the other way around. Treatment effects were consistent when microalbuminuria and macroalbuminuria developed. There are variations in UACR, although they were limited because of the little quantity of investigations. These results imply that SGLT2I may be more useful than DPP4-I in lowering albuminuria, which calls for greater study.

When DPP4-I were compared to controls, eGFR marginally dropped. A modest decrease in eGFR has been linked to DPP4-I treatment. Try out TECOS.[27] However, it's unclear if these modest are alterations in eGFR linked to any negative clinical outcomes. In addition, the maximumreports that made up our meta-analysis were <52 weeks. To monitor their long-term effects, the duration of the follow-up was restricted. In contrast to variations in renal function, DPP4-I seemed to lower the incidence of ESRD relative to the control. Renal decreasing function may benefit from it, according to three large cardiovascular outcome trials' findings.[28]

DPP4-I can shorten the duration of albuminuria after 52 weeks of therapy, according to a meta-analysis evaluating their impact on reverse osmosis (RO) in patients with T2DM. However, when equated to a placebo, the DPP4-I did not significantly raise eGFR or mortality. There seems to be a dearth of good research currently available to support the use of DPP4-I inhibitors to enhance RO and mortality in individuals with T2DM. Therefore, to substantiate the claims that its use will improve RO, more excellent randomized controlled trials are needed.

The current investigation has certain limitations. First off, the majority of the studies that made up our meta-analysis did not examine RO following pre-determined goals. Second, selection or attrition bias could have been present in nearly 40% of the trials. Third, there aren't many studies looking at incident albuminuria or ESRD. A head-to-head assessment of diverse DPP4-I is necessary to provide decisive proof regarding how particular drugs affect the outcomes being studied. As a result, care should be taken when interpreting the findings of our meta-analysis.

CONCLUSION

Overall, DPP4-I shows a significant role in RO in DM patients. There is no significant change in the adverse event profile was detected in the DPP4-I group as compared to the CG. However, more RCTs are required to confirm the influence of DPP4-I on RO in DM patients.

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ETHICAL DISCLOSURE

None required.

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