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Effect of glucagon-like peptide 1 receptor agonists on albuminuria in adult patients with type 2 diabetes mellitus: A systematic review and meta-analysis

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Abstract

Aims: To determine the effect of glucagon-like peptide 1 receptor agonists (GLP-1RAs) on albuminuria in adult patients with type 2 diabetes mellitus (T2DM).

Methods: Medline Ovid, Scopus, Web of Science, EMCARE and CINAHL databases from database inception until 27 January 2022. Studies were eligible for inclusion if they were randomized controlled trials that involved treatment with a GLP-1RA in adult patients with T2DM and assessed the effect on albuminuria in each treatment arm. Data extraction was conducted independently by three individual reviewers. The PRISMA guidelines were followed regarding data extraction and quality assessment. Data were pooled using a random effects inverse variance model and all analysis was carried out with RevMan 5.4 software. The Jadad scoring tool was employed to assess the quality of evidence and risk of bias in the randomized controlled trials.

Results: The initial search revealed 2419 articles, of which 19 were included in this study. An additional three articles were identified from hand-searching references of included reviews. Therefore, in total, 22 articles comprising 39 714 patients were included. Meta-analysis suggested that use of GLP1-RAs was associated with a reduction in albuminuria in patients with T2DM (weighted mean difference −16.14%, 95% CI −18.42 to −13.86%; $p < .0001$) compared with controls.

Conclusions: This meta-analysis indicates that GLP-1RAs are associated with a significant reduction in albuminuria in adult patients with T2DM when compared with placebo.

1 | INTRODUCTION

Diabetic kidney disease (DKD) is a major microvascular complication of type 2 diabetes mellitus (T2DM) with half of patients with T2DM developing DKD.[1] DKD is the leading cause of end stage kidney disease and the single strongest predictor of morbidity and mortality in patients with T2DM.[1-3] DKD is initiated because of chronic hyperglycaemia driving oxidative stress and inflammation, which results in structural and functional changes resulting in decreased renal function and albuminuria.[4,5]

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are a class of antidiabetic agent that have the potential to delay the progression of DKD.[2,4-6] It decreases blood glucagon levels, delays gastric emptying and regulates appetite to lower blood glucose levels and body weight. In experimental studies, GLP-1RAs have been shown to inhibit renal oxidative stress, fibrosis and apoptosis.[5,7,8]

To our knowledge, there are currently no published GLP1-RA trials with a primary endpoint of kidney events or enrolling only patients with DKD. Substantial insights into the renal-protective ability of GLP-1RAs have been provided by exploratory analysis of cardiovascular outcome trials.[9-14] Previous systematic reviews and meta-analysis have found that use of GLP-1RAs in patients with T2DM reduces composite kidney outcomes by 17% driven by a reduction in albuminuria, particularly macroalbuminuria.[15,16] This is important, as albuminuria itself is an independent predictor of early risk and prognosis of DKD and cardiovascular disease in patients with T2DM.[17]

Several studies have investigated the effect of GLP-1RAs on albuminuria.[9,10,12,13,18-35] A 2018 systematic review and meta-analysis by Luo et al. found that GLP-1RAs were associated with reduction in albuminuria of 13.85% in adult patients with T2DM compared with placebo or conventional therapy.[36] This review will examine 15 new additional studies that were not included along with examining the effects of four new GLP-1RAs (dulaglutide, efpeglenatide and semaglutide) on albuminuria. This review differs from the previous review as it will focus specifically on GLP-1RAs and will offer a more detailed comparison between the effects of individual GLP-1RAs on albuminuria, as opposed to a comparison between different classes of novel antidiabetic agents. The aim of this systematic review is to investigate the effect GLP-1RAs have on albuminuria in adult patients with T2DM.

2 | METHODS

This review was performed in accordance with the 2020 guideline for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[37] A review protocol was developed and formally registered in the PROSPERO database (CRD42021275635).

2.1 | Literature search strategy

To identify eligible studies, a literature search was performed using Medline Ovid (1946), Scopus (1970), Web of Science (1965), EMCARE (1995) and CINAHL (1981) databases from database inception until 11 August 2021. An additional search was conducted on 27 January 2022 to identify eligible articles that may have been published during manuscript preparation. Search terms were developed with assistance of a specialist medical librarian and individualized for databases. A Boolean search strategy was developed with controlled vocabulary searches and supplemented with keyword searches. The search strategy for Web of Science was as follows, with alterations made for alternative databases: ('Type 2 Diabetes Mellitus' OR T2DM OR 'non-insulin dependent diabetes' OR 'Type 2 diabetes' OR NIDMM OR 'adult onset diabetes mellitus' OR 'Type II Diabetes') AND ('GLP-1 RA' OR 'GLP-1RA' OR 'GLP-1 receptor agonist' OR 'glucagon like peptide-1 receptor agonist' OR 'glucagon like peptide 1 receptor agonist' OR 'glucagon like peptide-1 receptor' OR 'Glucagon like peptide 1 agonist' OR 'Glucagon-like-peptide-1' OR 'GLP-1 analogue' OR 'GLP-1 analog*' OR 'Glucagon like peptide-1 analogue' OR 'Glucagon like peptide-1 analog*' OR 'glucagon like peptide 1' OR GLP1 OR liraglutide OR saxenda OR victoza OR exenatide OR lixisenatide OR albiglutide OR dulaglutide OR semaglutide OR loxenatide OR efpeglenatide OR byetta OR adlyxin OR eperzan OR ozempic OR wegovy OR trulicity OR rybelsus OR AC2993 OR 'ITCA 650' OR LY2148568 OR AC002993 OR AC2993A OR nn2211 OR nn-2211 OR NNC901170 OR GSK716155 OR AVE0010 OR LY2189265 OR NN9535 OR NN9924) AND (albuminuria OR proteinuria OR 'urinary albumin excretion rate' OR 'urinary albumin excretion' OR UAE OR 'urinary albumin to creatinine ratio' OR 'urine albumin to creatinine ratio' OR UACR OR macroalbuminuria OR microalbuminuria OR 'diabetic nephropath*' OR 'diabetic kidney disease' OR 'kidney function' OR 'renal function' OR 'renal insufficiency' OR 'kidney failure' OR 'renal failure').

Titles and abstracts were screened to identify relevant articles, and potentially relevant articles had their full text examined to assess eligibility using predefined inclusion and exclusion criteria. Duplicate removal was first undertaken by EndNote20 then hand screening for any missed duplicates. These database searches were supplemented by hand searching reference lists of similar reviews identified in the search process. Two authors (DY and HS) undertook these searches on separate occasions and a consensus meeting was held during which discrepancies were resolved with a third reviewer (AK).

2.2 | Study selection

Studies were eligible for inclusion if they met the following criteria: (a) randomized controlled trial (RCT) design; (b) treatment with a GLP-1RA, compared with placebo or other conventional therapies; (c) adult participants (age ≥18 years) with T2DM; (d) assessment of the effects of a GLP-1RAs on albuminuria in each treatment arm and data reported for changes in albuminuria from baseline to follow-up; (e) treatment and follow-up duration no restriction; and (f) studies written in English.

Studies were excluded if: (a) non-RCT design; (b) inclusion of children, adolescents and patients with T1DM, renal haemodialysis, renal transplantation and acute kidney injury; (c) mean glycated haemoglobin A1c (HbA1c) <7.0%l; (d) mean estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (according to Modification of Diet in Renal Disease criteria); (e) body mass index (BMI) <18.5; (f) reported insufficient data on albuminuria, data regarding percentage changes in albuminuria not extractable or albuminuria not measured using urine albumin creatinine ratio (UACR) or urinary albumin excretion (UAE); and (g) abstract only with no full text.

2.3 | Data extraction

An initial data extraction spreadsheet was created and agreed upon in consultation with three authors (DY, HS, AK). Each reviewer extracted data independently and a consensus meeting was held to discuss extracted data and settle disagreements. The extracted data included baseline characteristics such as first author, year of publication, treatment regimen, follow-up duration and sample size. Patient information that was extracted included: mean age, sex distribution, diabetes duration, HbA1c, BMI, eGFR, systolic blood pressure (SBP) and albuminuria category (normoalbuminuria: UACR <30 mg/g, UACR <3.0 mg/mmol, or UAE <30 mg/day; microalbuminuria: 30 mg/g ≤ UACR ≤ 300 mg/g, 3.0 mg/mmol ≤ UAE ≤ 30 mg/mmol, or 30 mg/day ≤ UAE ≤ 300 mg/day; and macroalbuminuria: UACR >300 mg/day, UACR >30 mg/mmol, or UAE >300 mg/day). The outcomes of interest extracted were baseline, follow-up albuminuria levels and percentage changes in UACR or UAE. Data presented in figures only were extracted via WebPlotDigitizer.

2.4 | Quality assessment

The Jadad scoring tool was employed to assess quality of evidence and risk of bias in RCTs. Studies were assessed on the presence randomization and randomization procedure, presence and appropriateness of blinding procedures and explanation for dropouts and withdrawals.[38] The total score was out of seven points. Studies scoring 4 or more points were considered high quality. Quality assessment was undertaken by two reviewers (DY and HS).

2.5 | Data synthesis and statistical analysis

In this meta-analysis the effect of GLP-1RAs on albuminuria was evaluated as percentage changes from baseline to final UACR or UAE in both intervention and control arms. If data were missing, we first attempted to contact authors to obtain any missing data. If data were still unusable or authors non-contactable the change was calculated (follow-up—baseline) and percentage change calculated (change/baseline × 100%). When standard deviations (SDs) were unreported, they were calculated according to mean difference, number of participants, 95% confidence intervals (CI), standard errors, *p* values, coefficients of variation or interquartile ranges (dividing the range by 1.35). If still unavailable, missing SDs were obtained from correlations according to the related formula with a correlation coefficient of 0.5. In addition, the SD for percentage changes was calculated by dividing the SD for change by the mean baseline value. For studies with more than one intervention arm, we combined relevant arms into a single treatment arm. All calculation methods are referred to in the Cochrane Handbook for Systematic Reviews of Interventions.[39]

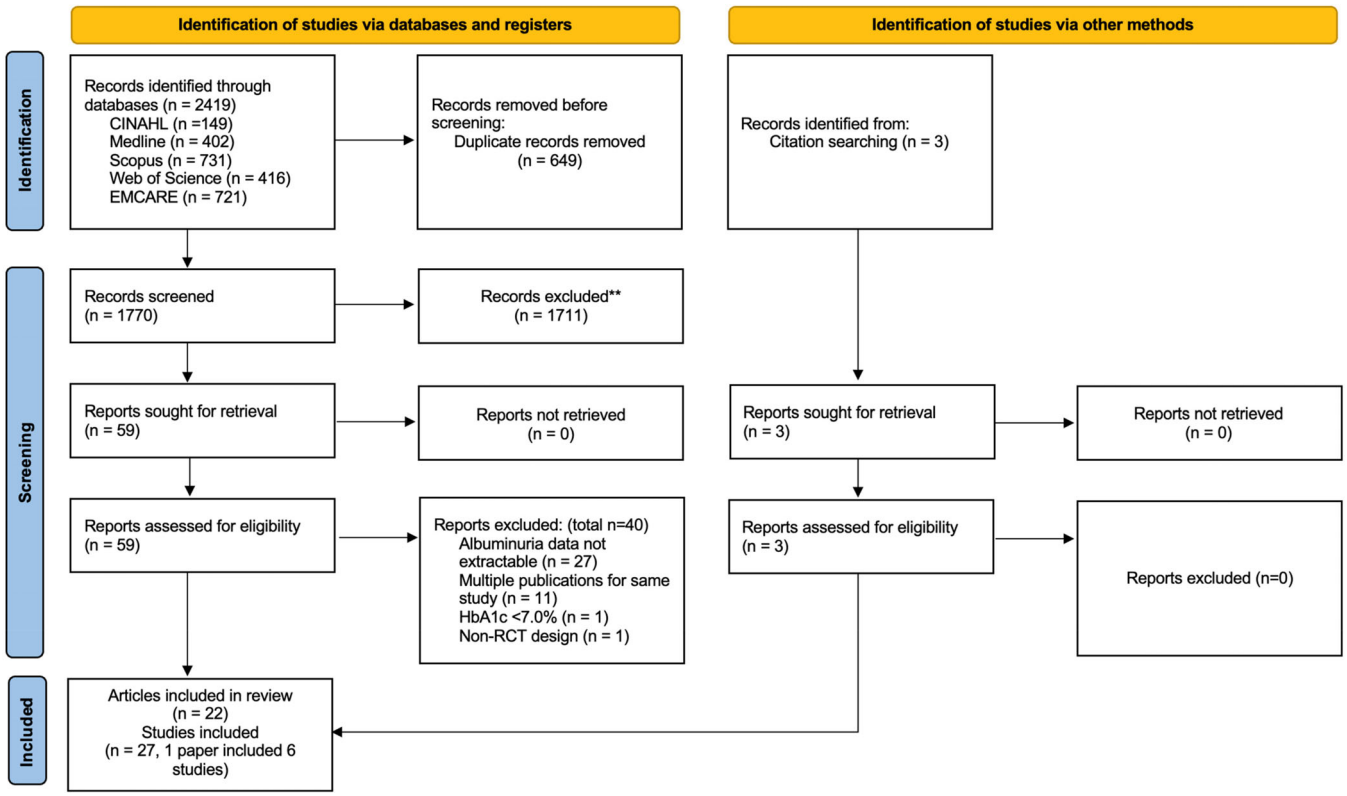


FIGURE 1 PRISMA flowchart describing the initial process of study selection and screening. HbA1c, glycated haemoglobin A1c; RCT, randomized controlled trial.

TABLE 1 Baseline characteristics of included studies

Author and year	Intervention	Control	Follow-up duration (weeks)	Sample size	Age (years)	Male (%)	Diabetes duration (years)	BMI	HbA1c (%)	eGFR (ml/min/1.73 m^2)	SBP (mmHg)	Albuminuria category	Ref.
Bergenstal 2010	Exenatide2 mg/week	Pioglitazone	26	Total n = 325Exenatide n = 160control n = 165	52.5 ± 10	51.7	6.0 ± 5.0	32.0 ± 5.5	8.6 ± 1.1	NR	126.5 ± 14	NR	24
Zhang 2012	Exenatide 5 mg BD to 10 mg BD	Glimepiride	16	Total n = 31Exenatide n = 13control n = 18	51.2 ± 14.5	74.2	4.1 ± 3.0	24.8 ± 2.0	8.9 ± 0.9	NR	137.7 ± 14.0	Micro	28
Derosa 2013	Exenatide 5 mg BD to 10 mg BD	Placebo	52	Total n = 171Exenatide n = 86 control n = 85	57.0 ± 7.5	51.5	0.6 ± 0.3	31.8 ± 1.6	8.0 ± 0.7	NR	132.2 ± 7.3	Micro	21
Davies 2015	Liraglutide 1.8 mg/day or 3.0 mg/day	Placebo	56	Total n = 846Liraglutide n = 634control n = 212	54.9 ± 10.6	50.2	7.3 ± 5.4	37.2 ± 6.7	7.9 ± 0.8	NR	129.4 ± 13.8	Normo	27
Miyagawa 2015	Dulaglutide 0.75 mg/ week	Placebo	26	Total n = 350 Dulaglutide n = 280control n = 70	57.3 ± 9.3	80.9	6.7 ± 5.5	25.5 ± 3.5	8.2 ± 0.8	NR	NR	Normo	30
Pfeffer 2015	Lixisenatide10 mg/day to 20 mg/day	Placebo	108	Total n = 6068Lixisenatide n = 3034 control n = 3034	60.3 ± 9.7	69.3	9.3 ± 8.3	30.2 ± 5.7	7.7 ± 1.3	75.5 ± 21.4	129.5 ± 17.0	Normo	9
Von Scholten 2015	Liraglutide 1.2 mg/day or 1.8 mg/day	Untreated	52	Total n = 30Liraglutide n = 23Liraglutide n = 7	61.5 ± 9.9	73.3	6.8 ± 11.1	31.9 ± 4.5	7.6 ± 1.3	98.6 ± 25.0	133.3 ± 12.6	Macro	29
Davies 2016	Liraglutide 1.8 mg	Placebo	26	Total n = 277Liraglutide n = 140 control n = 137	67.2 ± 8.2	50.5	15.1 ± 8.3	33.9 ± 5.4	8.0 ± 0.8	45.4 ± 10.9	136.0 ± 14.6	Macro	25
Tonneijick 2016	Exenatide 10 mg	Placebo	0	Total n = 52 Exenatide n = 24 control n = 28	62.6 ± 7.1	75.0	7.0 ± 5.4	31.1 ± 4.1	7.3 ± 0.7	91.9 ± 20.2	135.1 ± 14.6	Normo	18
Tonneijick Renal 2016	Liraglutide 1.8 mg/day	Placebo	12	Total n = 36Liraglutide n = 19control n = 17	63.0 ± 7.0	75.0	7.5 ± 6.0	31.4 ± 3.0	7.4 ± 0.7	80.9 ± 16.4	137.1 ± 15.8	Normo	33
Bouchi 2017	Liraglutide 0.3 mg to 0.9 mg/day	Insulin	36	Total n = 17Liraglutide n = 8control n = 9	58.6 ± 18.9	47.0	NR	28.0 ± 2.4	8.0 ± 0.6	68.5 ± 23.7	138.8 ± 16.9	Micro	32
Mann 2017	Liraglutide 1.8 mg/day	Placebo	208	Total n = 9340Liraglutide n = 4668 control n = 4672	64.3 ± 7.2	64.2	12.9 ± 8.0	32.5 ± 6.3	8.7 ± 1.6	80.4 ± NR	135.9 ± 17.7	Micro	10
Tonneijick 2017	Lixisenatide10 mg/day to 20 mg/day	Insulin Glulisine	8	Total n = 35Lixisenatide n = 17control n = 18	61.5 ± 7.0	65.7	12.5 ± 6.8	31.5 ± 4.0	8.0 ± 9.2	85.4 ± 11.9	134.0 ± 15.9	Normo	31

TABLE 1 (Continued)

Author and year	Intervention	Control	Follow-up duration (weeks)	Sample size	Age (years)	Male (%)	Diabetes duration (years)	BMI	HbA1c (%)	eGFR (ml/min/1.73 m^2)	SBP (mmHg)	Albuminuria category	Ref.
Von Scholten 2017	Liraglutide 1.8 mg/day	Placebo	12	Total n = 54 Liraglutide n = 27control n = 27	65.0 ± 7.0	81.0	15.0 ± 7.0	31.9 ± 5.0	7.8 ± 1.1	75.7 ± 22.7	135.0 ± 18.0	Macro	20
Tuttle 2018	Dulaglutide0.75 mg or 1.5 mg/day	Insulin glargine	52	Total n = 576Dulaglutide n = 382 control n = 194	64.6 ± 8.6	52.3	18.1 ± 8.7	32.5 ± 5.2	8.6 ± 1.0	38.3 ± 14.2	136.9 ± 14.3	Micro	19
Gerstein 2019	Dulaglutide 1.5 mg/day	Placebo	260	Total n = 9901Dulaglutide n = 4949control n = 4952	66.2 ± 6.5	53.7	10.6 ± 7.2	32.3 ± 5.7	7.4 ± 1.1	76.9 ± 22.8	137.2 ± 16.8	Normo	12
Mosenzon 2019	Oral semaglutide 14 mg/day	Placebo	26	Total n = 324Semaglutide n = 163control n = 161	70.0 ± 8.0	48.0	14.0 ± 8.0	32.4 ± 5.4	8.0 ± 0.7	48.0 ± 10.0	137.5 ± NR	Normo	26
Wang 2019	Dulaglutide0.75 mg or 1.5 mg/day	Insulin glargine	52	Total n = 25Dulaglutide n = 16 control n = 9	61.9 ± 9.5	60.0	NR	25.0 ± 2.5	8.7 ± 1.3	NR	134.1 ± 13.0	Normo	23
Nakaguchi 2020	Liraglutide 0.9 mg/day	Empagliflozin	24	Total n = 61Liraglutide n = 30control n = 31	66.7 ± 9.2	68.8	18.9 ± 9.9	26.1 ± 4.3	8.06 ± 0.8	65.2 ± 20.7	138.8 ± 17.3	Micro	22
Gerstein 2021	Efpeglenatide 4 or 6 mg	Placebo	94	Total n = 4076Efpeglenatide n = 2717 control n = 1359	64.5 ± 8.2	67.0	15.4 ± 8.8	32.7 ± 6.2	8.9 ± 1.5	72.4 ± 22.4	134.9 ± 15.5	Normo	13
Van Ruiten 2021	Exenatide 10 μg BD	Placebo	16	Total n = 34 Exenatide n = 17 Control n = 7	63.2 ± 6.7	71.0	9.8 ± 6.5	32.1 ± 5.4	8.1 ± 3.2	84.9 ± 12.4	133.3 ± 12.0	Normo	μ35
Man 2020 SUSTAIN 1	Semaglutide 0.5 mg or 1 mg	Placebo	30	Total n = 387 Semaglutide n = 158 Placebo n = 129	53.7 ± 11.3	54.3	1.9 ± 4.2	32.9 ± 7.7	8.1 ± 0.9	99.0 ± 26.4	128.8 ± 13.2	Normo	34
Man 2020 SUSTAIN 2	Semagltide 0.5 mg or 1.0 mg	Sitagliptin 100 mg	56	Total n = 1225 Semaglutide n = 818 Sitagliptin n = 407	55.1 ± 10.7	50.6	5.4 ± 4.6	32.5 ± 6.2	8.1 ± 0.9	100.0 ± 23.1	132.7 ± 14.9	Normo	34
Man 2020 SUSTAIN 3	Semaglutide 1.0 mg	Exenatide XR 2.0 mg	56	Total n = 809 Semaglutide n = 404	56.6 ± 10.7	55.3	8.1 ± 5.7	33.8 ± 6.7	8.3 ± 1.0	100.5 ± 23.6	133.5 ± 14.6	Normo	34

(Continues)

TABLE 1 (Continued)

Author and year	Intervention	Control	Follow-up duration (weeks)	Sample size	Age (years)	Male (%)	Diabetes duration (years)	BMI	HbA1c (%)	eGFR (ml/min/1.73 m^2)	SBP (mmHg)	Albuminuria category	Ref.
				Exenatide n = 405									
Man 2020 SUSTAIN 4	Semaglutide 0.5 mg or 1.0 mg	Insulin glargine	30	Total n = 1082 Semaglutide n = 722 Insulin n = 360	56.5 ± 10.4	53.0	7.3 ± 5.5	33.0 ± 6.5	8.2 ± 0.9	98.5 ± 26.6	132.1 ± 15.3	Normo	34
Man 2020 SUSTAIN 5	Semaglide 0.5 mg or 1.0 mg	Placebo	30	Total n = 396 Semaglutide n = 263 Placebo n = 133	58.8 ± 10.1	56.1	12.0 ± 7.4	32.2 ± 6.2	8.4 ± 0.8	91.3 ± 25.0	134.8 ± 16.0	Normo	34
Mann 2020 SUSTAIN 6	Semaglutide 0.5 mg or 1.0 mg	Placebo	104	Total n = 3286 Semaglutide n = 1642 Placebo n = 1644	64.6 ± 7.4	60.7	12.9 ± 7.9	32.8 ± 6.2	8.7 ± 1.5	76.1 ± 26.5	135.6 ± 17.2	Micro	34

Note: Data (age, BMI, diabetes duration, HbA1c, eGFR, SBP) reflects the average baseline level. Data are expressed as mean ± standard deviation.
Abbreviations: BD, twice a day; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A_{1c}; macro, macroalbuminuria; micro, microalbuminuria; normo, normoalbuminuria; NR, not reported; SBP, systolic blood pressure.

Data regarding percentage changes in albuminuria was used to generate weighted mean differences (WMDs) and 95% CIs. A random-effects inverse variance model was employed for synthesizing data as clinical and statistical heterogeneity was anticipated. Forest plots were used to represent results. Heterogeneity was quantified using the I^2 statistic and an I^2 value of 50-75% was considered to indicate moderate heterogeneity and values >75% were considered high heterogeneity.[40] Subgroup analysis based on the specific GLP-1RAs, type of control, patients' age, diabetes duration, baseline HbA1c, BMI, eGFR, SBP, Jadad score, sample size and albuminuria categories was performed to analyse potential sources of heterogeneity. Publication bias was assessed using funnel plots. Leave-one-out studies were used for sensitivity analysis. All statistical analysis was performed with RevMan 5.4 software. A value of $p \leq .05$ was considered statistically significant.

3 | RESULTS

3.1 | Search results

Initial searches across all databases identified 2419 studies of which 649 were removed as duplicates. Title and abstract screen were conducted for 1770 articles and 1711 were excluded. The full texts of 59 articles were screened of which 40 were excluded because of following reasons: data for albuminuria not extractable (n = 27), multiple publications for the same study (n = 11), HbA1c <7% (n = 1) and non-RCT (n = 1). A further three articles were identified from examining the references of previous reviews and had all three articles had their full texts examined and were included in the final review. Therefore, in total, 22 papers featuring 27 studies involving 39 714 patients with T2DM were included in this systematic review (one paper was a post-hoc analysis featuring six studies).[9,10,12,13,18-35] All studies were included in the meta-analysis. The initial study selection and screening process is described in the PRISMA flowchart in Figure 1.

3.2 | Characteristics of included studies

Baseline characteristics of included studies are summarized in Table 1. Studies were reported from 2010 to 2021. The sample sizes of GLP-1RA intervention and control groups ranged from 8 to 4949 and 7 to 4952 respectively. The average age of participants ranged from 51.2 to 70.0 years and proportion of males ranged from 47.0% to 80.9%. Baseline HbA1c levels ranged from 7.3 to 8.9%, baseline BMI ranged from 24.9 to 33.9 kg/m^2, mean baseline eGFR ranged from 38.3 to 100.5 ml/min/1.73 m^2. The range of follow-up was from 0 to 260 weeks. In total, 17 studies were placebo controlled, five studies used insulin as the control and five employed other antidiabetic agents (pioglitazone, glimepiride, exenatide and empagliflozin) as controls. Five studies examined the effect of exenatide, eight examined liraglutide, six studies examined injected subcutaneous semaglutide, four studies examined dulaglutide, two studies examined lixisenatide,

TABLE 2 Baseline and follow-up albuminuria levels of included studies

		GLP-1 receptor agonist				Control				
Study	**Index**	**Baseline**	**Follow-up**	**Change**	**% Change**	**Baseline**	**Follow-up**	**Change**	**% Change**	**Ref.**
Bergenstal 2010	Log UACR (mg/g)	NR	NR	NR	−16.1 ± 19.4	NR	NR	NR	−4.0 ± 21.6	24
Zhang 2012	UAE (mg/day)	107.0 ± 71.0	65.0 ± 47.0	−42.0 ± 62.6	−39.3 ± 58.5	111.0 ± 74.0	106.0 ± 75.0	−5.0 ± 74.5	−4.6 ± 67.1	28
Derosa 2013	UAE (mg/day)	98.2 ± 52.9	71.8 ± 32.6	−26.4 ± 46.2	−26.9 ± 47.0	93.6 ± 47.1	76.2 ± 35.4	−17.4 ± 42.5	−18.6 ± 45.4	21
Davies 2015	Log UACR (mg/mmol)	1.0 ± 1.6	NR	NR	−15.8 ± 3.8	1.0 ± 1.6	NR	NR	−2.3 ± 1.0	27
Miyagawa 2015	UACR (mg/g)	12.4 ± NR	NR	−1.77 ± 4.0	−14.3 ± 32.3	10.62 ± NR	NR	0.89 ± 2.0	8.4 ± 18.8	30
Pfeffer 2015	UACR (mg/g)	10.0 ± 16.3	11.9 ± 26.7	1.9 ± 23.3	19.0 ± 233.0	10.4 ± 19.8	13.4 ± 34.7	3.0 ± 30.1	28.8 ± 289.4	9
Von Scholten 2015	Log UAE (mg/day)	25.5 ± 30.4	18.6 ± 27.3	NR	−27.1 ± 45.1	48.6 ± 137.3	53.5 ± 228.1	NR	10.1 ± 42.7	29
Davies 2016	UACR (mg/g)	55.5 ± 4.2	48.3 ± 2.1	−7.2 ± 2.4	−13.0 ± 28.9	69.8 ± 4.0	73.3 ± 3.7	3.5 ± 3.2	5.0 ± 18.5	25
Tonneijick 2016	UACR (mg/mmol)	0.9 ± 2.0	0.8 ± 1.3	−0.1 ± 1.8	−10.8 ± 193.5	1.0 ± 1.0	0.6 ± 0.4	−0.4 ± 0.9	−38.5 ± 86.5	18
Tonneijick renal 2016	UACR (mg/mmol)	1.0 ± 0.6	0.9 ± 0.6	−0.1 ± 0.6	−10 ± 60	1.1 ± 3.3	2.1 ± 5.9	1.0 ± 5.1	87.6 ± 463.6	33
Bouchi 2017	UACR (mg/g)	220.0 ± 243.0	32.0 ± 145.9	−188.0 ± 211.9	−85.5 ± 96.3	254.0 ± 294.8	226.0 ± 1005.9	−28.0 ± 895.7	−11.0 ± 352.6	32
Mann 2017	UACR (mg/g)	21.0 ± NR	24.1 ± NR	3.1 ± 45.5	14.8 ± 216.7	21.0 ± NR	28.5 ± NR	7.5 ± 110.1	35.7 ± 524.3	10
Tonneijick 2017	UACR (mg/mmol)	0.45 ± 1.4	0.67 ± 1.2	0.22 ± 1.3	48.9 ± 288.9	0.93 ± 1.0	0.81 ± 1.2	−0.1 ± 1.1	10.8 ± 118.3	31
Von Scholten 2017	Log UAE (mg/day)	183.0 ± 340.0	135.0 ± 172.6	NR	−26.0 ± 48.0	181.0 ± 199.3	199.0 ± 333.3	NR	9.0 ± 35.4	20
Tuttle 2018	UACR (mg/g)	223.6 ± 674.6	NR	NR	−21.3 ± 98.8	195.6 ± 729.6	NR	NR	−13.0 ± 110.1	19
Gerstein 2019	UACR (mg/mmol)	1.8 ± 4.4	NR	NR	−0.04 ± 71.8	1.88 ± 4.9	NR	NR	17.0 ± 71.8	12
Mosenzon 2019	UACR (mg/g)	19.2 ± 79.6	NR	NR	−14.0 ± 142.0	14.1 ± 63.2	NR	NR	19.0 ± 158.9	26
Wang 2019	UACR (mg/g)	2.7 ± 4.2	3.3 ± 2.8	NR	22.2 ± 137.0	3.8 ± 8.4	4.6 ± 3.9	NR	21.1 ± 192	23
Nakaguchi 2020	UACR (mg/g)	52.9 ± 362.8	33.3 ± 276	−5.3 ± 52.2	−10.0 ± 98.7	66.6 ± 84.1	32.1 ± 59.5	−12.9 ± 51.0	−19.4 ± 76.5	22
Gerstein 2021	Log UACR (mg/g)	28.3 ± 81.9	NR	NR	−37.0 ± 53.7	28.3 ± 71.9	NR	NR	−19.0 ± 38.3	13
Van Ruiten 2021	UACR (mg/mmol)	1.0 ± 1.6	NR	NR	−15.6 ± 46.7	0.7 ± 1.9	NR	NR	−11.0 ± 52.8	35
Man 2020 SUSTAIN 1	UACR (mg/g)	13.7 ± 35.2	11.8 ± 11.5	−1.9 ± 31.1	−13.9 ± 227.0	13.7 ± 35.2	14.9 ± 14.2	1.2 ± 30.7	8.8 ± 224.1	34
Man 2020 SUSTAIN 2	UACR (mg/g)	15.5 ± 32.6	13.5 ± 11.9	−2.0 ± 28.6	−12.9 ± 184.5	15.5 ± 32.6	15.1 ± 14.9	−0.4 ± 28.3	−2.6 ± 182.6	34
Man 2020 SUSTAIN 3	UACR (mg/g)	15.4 ± 40.8	13.3 ± 13.8	−2.1 ± 35.9	−13.6 ± 233.1	15.4 ± 40.8	14.2 ± 13.3	−1.2 ± 36.0	−7.8 ± 233.8	34
Man 2020 SUSTAIN 4	UACR (mg/g)	14.7 ± 37.8	13.2 ± 11.2	−1.5 ± 33.6	−10.2 ± 228.6	14.7 ± 37.8	14.5 ± 12.1	−0.2 ± 33.4	−1.4 ± 227.2	34
Man 2020 SUSTAIN 5	UACR (mg/g	23.1 ± 86.2	18.0 ± 18.7	−5.1 ± 78.5	−22.1 ± 339.8	23.1 ± 86.2	28.8 ± 30.0	5.7 ± 75.8	24.7 ± 328.1	34
Mann 2020 SUSTAIN 6	UACR (mg/g)	38.6 ± 213.7	35.4 ± 43.5	−3.2 ± 195.6	−8.3 ± 506.7	38.6 ± 213.7	50.5 ± 73.4	11.9 ± 188.1	30.8 ± 487.3	34

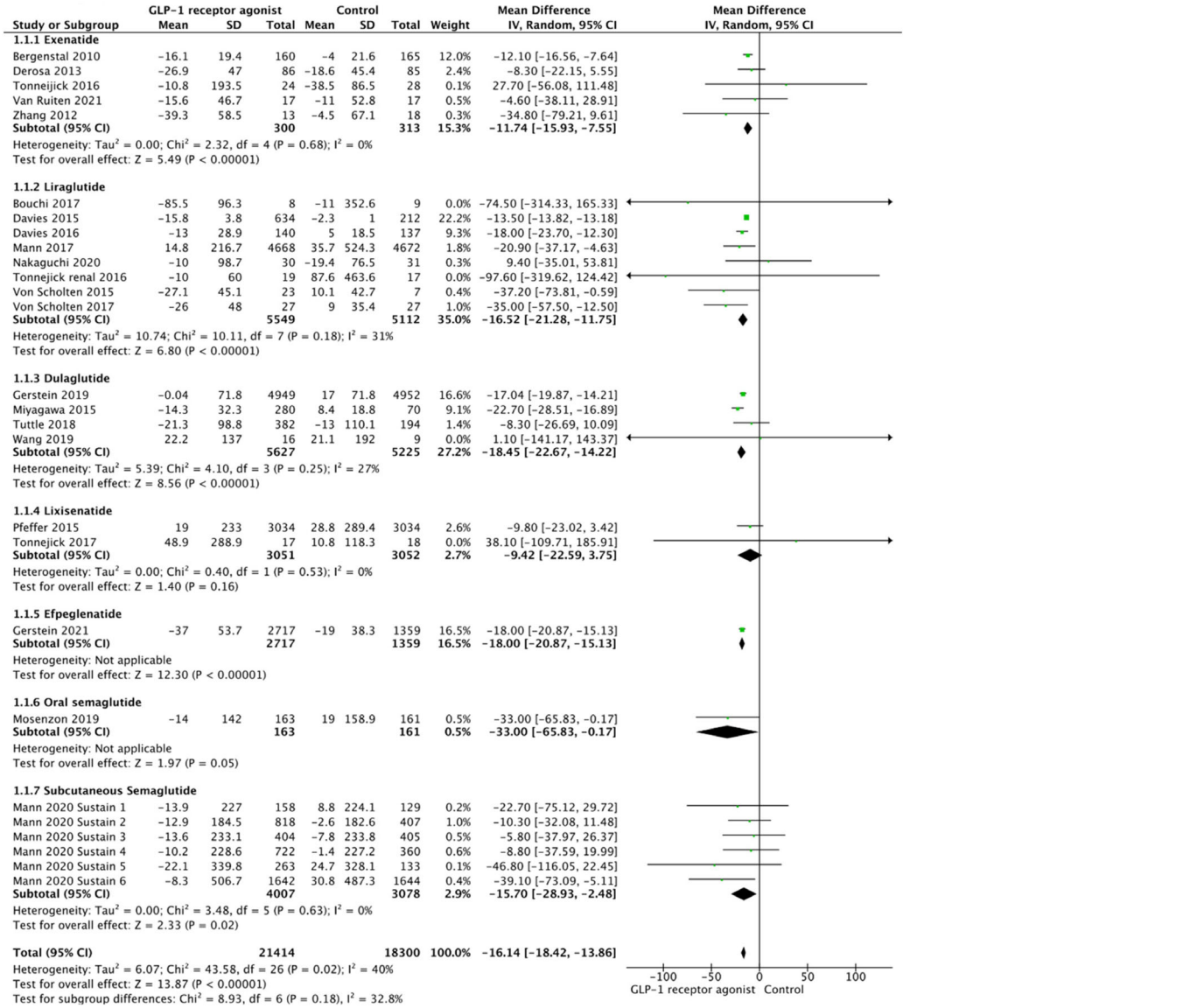
Note: Data are expressed as mean ± standard deviation.

Abbreviations: GLP-1, glucagon like peptide 1; Log, logarithm; NR, not reported; UACR, urine albumin to creatinine ratio; UAE, urine albumin excretion.

one study examined efpeglenatide and one examined the effect of oral semaglutide on albuminuria. Sixteen studies involved patients with normoalbuminuria, seven with microalbuminuria, three with macroalbuminuria and one did not report baseline albuminuria category. The Jadad score for each study is shown in Table S1. Scores ranged from 1 to 7 with the average being 5.2 Table S1.

3.3 | Effects of individual glucagon-like peptide 1 receptor agonists on albuminuria

The overall UACR/UAE changes from all 27 studies were extractable as outcomes, and albuminuria data for each individual study are presented in Table 2. In the pooled analysis of GLP-1RAs there was a significant reduction in albuminuria (WMD −16.14%, 95% CI −18.42 to −13.86%; $p < .00001$) compared with controls overall (Figure 2). Statistically significant reductions in albuminuria were seen with exenatide (WMD −11.74%, 95% CI −15.93 to −7.55%; $p < .00001$), liraglutide (WMD −16.52%, 95% CI −21.28 to −11.75%; $p < .0001$), dulaglutide (WMD −18.45%, 95% CI −22.67 to −11.75%; $p < .00001$), efpeglenatide (WMD −18.00%, 95% CI −20.87 to −15.13%; $p < .00001$), subcutaneous semaglutide (WMD −15.70%, 95% CI −28.93 to−2.48%; $p = .02$) and oral semaglutide (WMD −33.00%, 95% CI −65.83 to −0.17; $p = .05$). No statistically significant reduction in albuminuria was found in the lixisenatide subgroup (WMD −9.42%, 95% CI −22.59 to 3.75%; $p = .16$). There was an overall trend toward a direct association between GLP-1RA use and reduction in albuminuria in most trials. There was significant heterogeneity overall ($I^2 = 40$, $p = .02$).



GLP-1, glucagon-like peptide 1; SD, standard deviation; IV, inverse variance; CI, confidence interval.

FIGURE 2 Forest plot of the percentage change in albuminuria among patients randomized to different types of GLP-1RAs compared with controls. CI, confidence interval; GLP-1, glucagon-like peptide 1; IV, inverse variance; SD, standard deviation.

Meanwhile, subgroup analysis revealed there were significant differences in reduction in albuminuria between the use of exenatide and dulaglutide ($p = .03$), exenatide and efpeglenatide ($p = .02$). No significant differences in reduction of albuminuria were present between the use exenatide and liraglutide, exenatide and semaglutide, liraglutide and dulaglutide, liraglutide and efpeglenatide, liraglutide and semaglutide, dulaglutide and efpeglenatide, and between efpeglenatide and semaglutide ($p > .05$, Table S2).

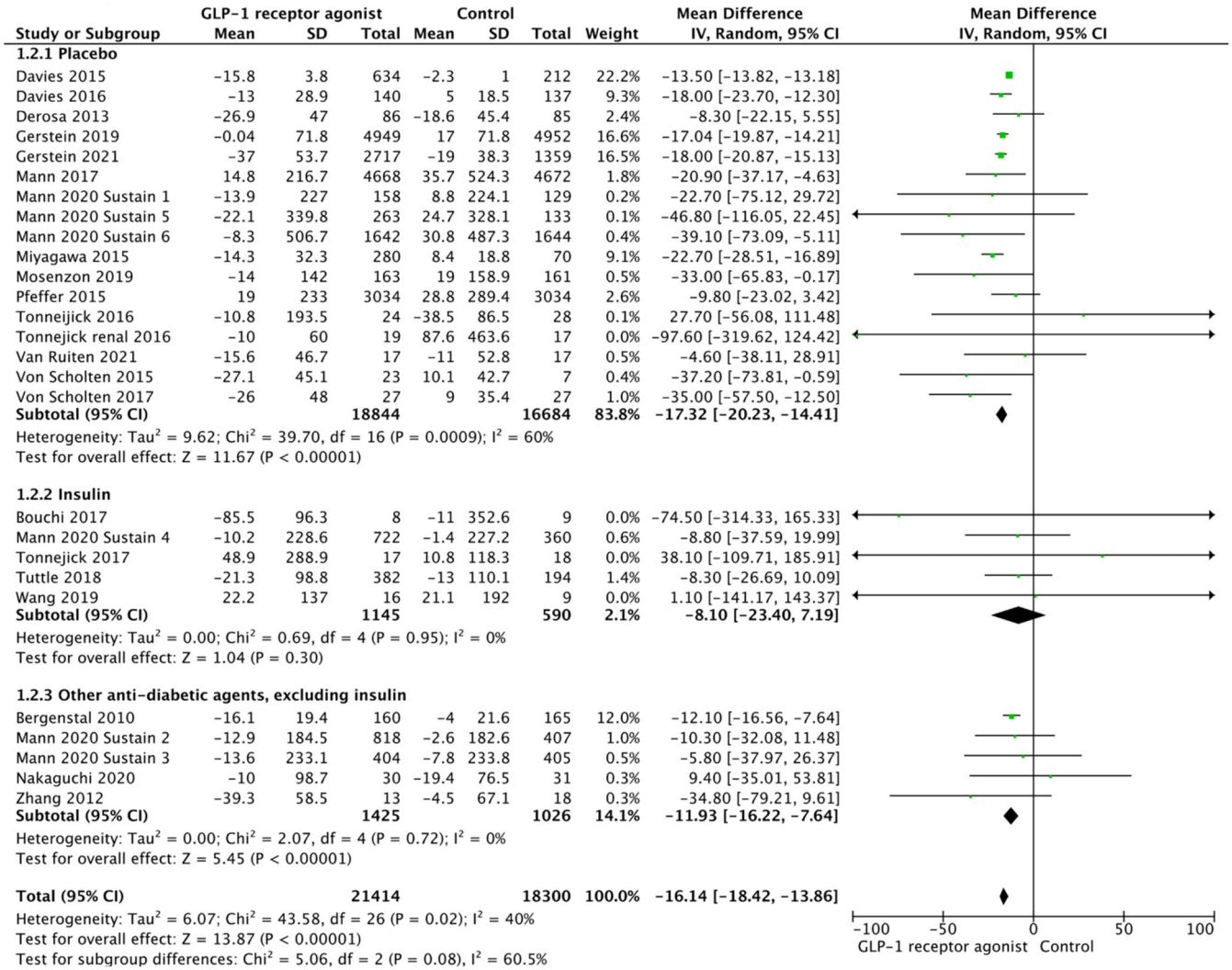
3.4 | Effect of type of control employed on albuminuria

Reductions in albuminuria were significant only when GLP-1RAs were compared with placebo (WMD −17.32%, 95% CI −20.23 to −14.41%; $p < .00001$) or other antidiabetic agents, excluding insulin (WMD −11.93%, 95% CI −16.22 to −7.64%; $p < .00001$). When GLP-1RAs were compared with insulin there was no statistically significant reduction in albuminuria (WMD −8.10%, 95% CI −23.40 to 7.19%; $p = .30$) (Figure 3.)

There was no statistically significant difference in reduction of albuminuria between all three groups ($p = .08$). No statistically significant difference in reduction of albuminuria was seen when comparing the use of placebo and insulin as a control ($p = .25$) and between the use of insulin or other antidiabetic agents, excluding insulin as a control ($p = .64$). However, the difference in reduction of albuminuria when GLP-1RAs were compared with placebo versus other antidiabetic agents, excluding insulin was significant ($p = .04$).

3.5 | Effect of baseline renal parameters on albuminuria

When stratified by baseline albuminuria categories, significant reductions were observed in all three groups of normoalbuminuria (WMD



GLP-1, glucagon-like peptide 1; SD, standard deviation; IV, inverse variance; CI, confidence interval.

FIGURE 3 Forest plot of the percentage change in albuminuria among patients randomized to different types controls compared with GLP-1RAs. CI, confidence interval; GLP-1, glucagon-like peptide 1; IV, inverse variance; SD, standard deviation.

−16.41%, 95% CI −19.25 to −13.58% $p < .00001$), microalbuminuria (WMD −14.07%, 95% CI −22.57 to −5.57 $p = .001$) and macroalbuminuria (WMD −23.66%, 95% CI −36.07 to −11.26, $p < .0002$). There was no statistically significant difference in reduction of albuminuria between the groups ($p = .45$, Table S2). Similarly, when stratified by baseline eGFR statistically significant reductions were observed in all groups of patients with no significant difference in reduction between the groups ($p = .87$, Table S2).

3.6 | Impact of other baseline characteristics on albuminuria

When stratified by SBP, significant reduction in albuminuria was seen in the subgroups >130 mmHg (WMD −17.45%, 95% CI −19.27 to −15.62; $p < .00001$) and ≤130 mmHg (WMD −13.49%, 95% CI −13.81 to −13.17%, $p < .00001$). Moreover, there was a significant difference in reduction of albuminuria between the two groups ($p < .00001$, Table S2). Similarly significant reduction was also seen in both subgroups when stratified by BMI >30 (WMD −15.45, 95% CI −17.57 to −13.32; $p < .00001$) and BMI ≤30 (WMD −22.36%, 95% CI −28.06 to −16.66; $p < .00001$). A significant difference in reduction of albuminuria of between the two groups was also present ($p = .03$, Table S2). When stratified by other baseline characteristics of age, HbA1c, diabetes duration, Jadad score, duration of follow-up, sample size or type of measurement, no significant difference in reduction of albuminuria was found ($p > .05$, Table S2).

3.7 | Risk of bias across studies and sensitivity analysis

Leave-one-out sensitivity analysis showed that average changes in albuminuria did not vary substantially with exclusion of any individual study. Visual analysis of the funnel plot (Figure S1) indicated slight asymmetry.

4 | DISCUSSION

The main finding of this systematic review and meta-analysis is that use of GLP-1RAs in adult patients with T2DM was associated with a significant overall reduction in albuminuria compared with placebo. This result is largely in keeping with the previous meta-analysis by Luo et al.[36] Our study included 15 new studies and four new GLP-1RAs thereby reinforcing the association between use of GLP-1RAs and reduced albuminuria in adult patients with T2DM. However, in our study higher heterogeneity was observed than previously identified (40% vs. 11%).

According to our findings the possible sources of heterogeneity could be because of a patient's baseline SBP, baseline BMI and the specific type of GLP-1RA used. Subgroup analysis suggested that all GLP-1RAs except lixisenatide were associated with significant reduction in albuminuria. This could be because of the trial design as in one trial all patients were at high cardiovascular risk, which has a known link to poorer renal outcomes and another study compared lixisenatide with insulin glulisine.[9,31] Results from this meta-analysis has shown that GLP-1RAs only yield statistically significant reductions in albuminuria when they are compared with placebo or other anti-diabetic agents but not insulin and hence could explain the non-significant reduction in albuminuria that trial.[31]

Our study also suggested that differences in albuminuria reduction were present between the following GLP-1RAs: exenatide and dulaglutide, exenatide and efpeglenatide. This may be because of differences in individual pharmacological properties. Several mechanisms have been proposed to explain the albuminuria reducing effect of GLP-1RAs. GLP-1RAs increase intrarenal cAMP generation and protein kinase A activation, which inhibits NADPH oxidase to reduce oxidative stress brought about by chronic hyperglycaemia thereby reducing albuminuria.[5,8,41] GLP-1RAs have also been shown to inhibit Na/H exchanger 3 in proximal tubules and showed to induce natriuresis and diuresis thereby reducing sodium retention and potentially reducing SBP.[5,42,43] Targeting the renin-angiotensin-aldosterone system (RAAS) and reducing SBP has traditionally been a key strategy to delay progression of DKD.[4] Studies have shown that GLP-1RAs increase BP acutely but lower BP after prolonged treatment and this antihypertensive effect may provide additional renal protection in addition to lowering blood glucose.[5,43] Higher SBPs in patients with T2DM are associated with poorer renal outcomes because of earlier renal damage. Therefore, it is possible that the more significant reduction in albuminuria observed in studies with baseline SBP >130 mmHg compared with those <130 mmHg may be explained by the ability of GLP-1RAs to also lower SBP. Hypertension, cardiovascular disease and T2DM are chronic conditions that often coexist together. The potential of GLP-1RAs to mediate renal protection through lowering SBP in addition to other mechanisms may prove highly beneficial in the management of patients with T2DM and preventing increasing rates of morbidity and mortality.

Increasing evidence has suggested that GLP-1RAs mediate protective actions on the kidney independent of glucose-lowering effects.[5,44] This may in part explain the non-significant reduction of albuminuria when GLP-1RAs were compared with insulin. It may be true that insulin mediates renal protection through primarily lowering glucose levels while GLP-1RAs mediate renal protection through the described mechanisms as well as targeting obesity, reducing inflammation and renal hypoxia.[8,43,45] Given this variety of mechanisms in which GLP-1RAs may mediate renal protection, specific GLP-1RAs will probably exert greater effects on certain mechanisms depending on the unique pharmacological properties of the drug. This may also serve to explain the significant differences in lowering albuminuria between different GLP-1RAs. However, while differences observed may be because of pharmacological properties of different GLP-1RAs, it is important to consider variable patient characteristics and trial heterogeneity. Any claims of superiority for any GLP-1RA should only be made with further research with prospective head-to-head comparative trials. Interestingly, it was

observed that non-obese subjects had a greater reduction in albuminuria compared with obese counterparts. It is known that GLP-1RAs are effective weight loss agents through their actions in controlling gut motility and appetite.[46,47] However, dosages of GLP1-RAs used for weight loss are significantly higher than those used in the management of T2DM and hence it may be that GLP-1RA exerts less effect on obesity at lower doses and its albuminuria reducing effects in T2DM are mainly mediated through other mechanisms as described. Therefore, further studies investigating the pharmacological mechanisms of renal protection mediated by specific GLP-1RAs will serve to improve understanding in this area and help to individualize therapy for patients with T2DM.

Despite the positive findings of this study, there were several limitations. First, the follow-up duration was varied and relatively short for many studies. Secondly, some changes in albuminuria were not directly extractable and although data were calculated in accordance to well accepted methods, certain biases in extraction and interpretation of graphical data are inevitable. We have also ignored the use of RAAS inhibitors or other renoprotective agents such as SGLT2 inhibitors. This is an important limitation as SGLT2 inhibitors, in particular, have a well-documented effect on albuminuria to a magnitude higher than reported in this study.[48] While we aimed to investigate the effect of GLP-1RAs compared with other antidiabetic agents other than insulin, only one study directly compared a GLP-1RA with an SGLT2 inhibitor.[22] Future studies comparing specific agents of these two classes of drugs will be beneficial. Moreover, RAAS inhibitors are often administered to patients with DKD. However, given that GLP-1RAs may also reduce SBP and induce natriuresis, it is possible that the concomitant treatment with both GLP-1RAs and RAAS inhibitors will further influence albuminuria outcomes. Further studies into this area will improve our understanding for the care of patients with DKD.

The study also examined albuminuria as an individual measure. Often clinically a combination of renal parameters such as eGFR and serum creatinine are used to make treatment decisions. Although a reduction in albuminuria was seen this effect was only relatively modest, except for the use of oral semaglutide. Further investigation as to whether this results in clinically significant outcomes is needed to balance potential side effects.

Finally, results from this meta-analysis are only applicable to adult patients with T2DM and not younger patients with T2DM or the general population, and our study did observe publication bias. Overall, despite these limitations, our findings are in keeping with previous results. Future studies to help address these limitations and clarify aspects described previously will serve to improve the understanding of the relationship between GLP-1RAs and albuminuria and improve clinical outcomes for patients with T2DM.

5 | CONCLUSION

In conclusion, this meta-analysis indicates that GLP-1RAs, particularly exenatide, liraglutide, dulaglutide, efpeglenatide and semaglutide are associated with a reduction in albuminuria in adult patients with T2DM compared with placebo. With continued research, GLP-1RAs will probably play a greater role in the management of T2DM, in particular, by delaying the progression of DKD.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the manuscript and supplementary material of this article

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