BMC Endocrine Disorders

RESEARCH

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Influence of glucagon-like peptide-1 receptor agonists on renal parameters: a meta-analysis of randomized controlled trials

Wenjing Li[1,2†], Xiaoyan Liang[3†], Na Sun[1] and Daqing Zhang[1,4*]

Abstract

Aims To verify the influence of glucagon-like peptide-1 receptor agonists (GLP-1 RA) on renal function parameters in type 2 diabetes based on well-known randomized controlled trials (RCTs).

Methods PubMed, Cochrane, Web of Science, Embase, and grey literature were searched for RCTs published until December 24, 2024. The quality of the RCTs was assessed using the Cochrane risk-of-bias tool. Weighted mean differences (WMD) and 95% confidence intervals (CIs) were calculated for continuous variables using meta-analysis. The primary outcomes were composite renal function parameters, including serum creatinine (Cr) levels, estimated glomerular filtration rate (eGFR), urinary albumin excretion (UAE), and urinary albumin-to-creatinine ratio (UACR).

Results Pooled data from 24 studies revealed that GLP-1 RA positively influenced renal outcomes in the type 2 diabetes group to some extent compared with that in the control group. GLP- 1 RA decreased serum creatinine levels (WMD=-0.10, 95%CI -0.19 to -0.01, $I^2=33\%$, $P<0.05$), eGFR(WMD = 0.54, 95% CI 0.19 to 0.90, $I^2=27\%$, $P<0.05$), UAE (WMD=-11.92, 95% CI −23.50 to −0.33, $I^2=0\%$, $P<0.05$) and UACR (WMD: −1.01 mg/g, 95% CI:−1.68, -0.34, $I^2=15\%$, $P<0.05$) in the type 2 diabetes group.

Conclusion GLP-1 RA treatment significantly elevated eGFR, decreased the UACR, and positively influenced renal function outcomes in the type 2 diabetes group.

Clinical trial number Not applicable.

Keywords GLP-1 RA, UAE, Cr, eGFR, UACR

Introduction

Diabetes has become widespread, with approximately 463 million people diagnosed with diabetes mellitus (DM) over recent years. By 2045, diabetes will affect at least 700 million people [1]. Approximately 25-30% of patients with type 2 DM (T2DM) will develop chronic kidney disease (CKD), and diabetes is currently the primary cause of end-stage kidney disease requiring kidney replacement therapy [2]. Patients with diabetic kidney disease (DKD) often have high rates of cardiovascular events, hospitalizations, infections, and mortality [3–5].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i)

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are the most commonly used drugs for treating diabetes. Relevant randomized controlled trials (RCTs) have demonstrated that clinical chronic renal events can be decreased by intensive glucose control [6], blood pressure decline, and the renin-angioten-sin-aldosterone system (RAAS) antagonized by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. Even with recommended RAAS blockers, patients with DKD are at a substantial risk of cardiovascular morbidity and mortality [7]. A previous study has reported that, the use of medications such as GLP-1RAs and SGLT2i delays or minimizes microvascular and macrovascular damage [8].

The American Diabetes Association 2023 guidelines recommend the use of metformin in combination with SGLT2i or GLP-1 RA in patients with established atherosclerotic cardiovascular diseases, heart failure, or CKD [9]. Recent advances have shown that SGLT2i [10, 11] could prevent the development of major kidney events. Although previous network meta-analyses have indicated the superiority of SGLT-2i over GLP-1RA in improving renal outcomes [12, 13], recent studies have demonstrated the positive effects of GLP-1 RA on renal function outcomes. The AWARD-7 trial showed that duraglutide delayed estimated glomerular filtration rate (eGFR) decline compared with insulin glargine in patients with T2DM at 52 weeks of follow-up [14]. In previous clinical studies, liraglutide improved heart and kidney outcomes and reduced cardiovascular events and all-cause mortality in parents with T2DM [15]. Weekly subcutaneous injections reduce the risk of serious cardiovascular or renal events, even in combination with cardiovascular or renal disease [16]. Previous meta-analyses have shown that GLP-1 RAs reduced compound renal endpoints (renal outcomes, including the development of massive proteinuria, a doubling of serum creatinine, a reduction in eGFR of at least 40%, kidney replacement therapy, or death from kidney disease) by 21% (hazard ratio [HR]0.79 [95% confidence interval [CI]0.73–0.87]; $p < 0{\cdot}0001$) in patients with T2MD [17]. However, opinions regarding GLP-1 RA differ. A recent meta-analysis has shown that GLP-1 RA did not significantly reduce renal outcomes compared with placebo [18]. Exenatide-related research has not shown improved GFR in patients with T2DM with normal renal function [19].

As a new medicine intervenes with the outcome of T2DM, GLP-1RAs have demonstrated inconsistent effects on renal function., Therefore, this meta-analysis aimed to examine the influence of GLP-1 RA on renal function.

Methods

Search strategy

This study followed the analytical strategy of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [20]. We systematically searched PubMed, the Web of Science, and the Cochrane for articles published up to December 24, 2024. The search keywords are provided in Appendix File S1.

Inclusion and exclusion criteria

The study inclusion criteria were as follows: selected in peer-reviewed journals; the population of the studies included were samples of adult individuals and no gender differences were found; RCTs in groups with T2DM with any condition or disease and were published in the English language; compared GLP-1 agonists (liraglutide, exenatide, semaglutide, dulaglutide, albiglutide, and lixisenatide) with placebo or other hypoglycemic agents; they compared the main renal outcomes, including serum creatinine (Cr)levels, eGFR, albumin-to-creatinine ratio (UACR), and urinary albumin excretion (UAE).

The exclusion criteria were as follows: narrative or comprehensive reviews, theoretical papers, meta-analyses, conferences, and guidelines; non T2DM studies, or non-RCTs; not peer-reviewed or formally open papers; and eGFR< 15 ml/min/1.73 m^2.

Data extraction

The following information was collected from the included studies: first author; publication year; study design; treatment duration; number of patients in the treatment and control groups; treatment medication and dose; sex, and serum creatinine level, eGFR, uACR, UAE rate.

Quality assessment

The quality of the included trials was analyzed using the Cochrane criteria relying on the risk of bias table, considering random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, incomplete outcome data, reporting biases, and other biases. Following the Cochrane Handbook recommendations, based on the original text, the risk of bias was classified as "low, high, or unclear".

Quantitative data analysis

The meta-analysis outcomes were analyzed using the Review Manager statistical software version 5.3. The effect size was obtained as follows: A random-effects model and mean ± standard deviation (SD)for the meta-analysis. SD values were calculated when the outcome data were reported with a 95% CI(or interquartile range) [21]. Supposing that the standard error of the mean (SEM) was provided in the primary document, SD was

acquired as follows: SD = SEM × √(n). To maintain the authenticity of the intervention and control groups, they were divided accordingly [22]. Effect sizes were assessed using weighted mean difference (WMD) and 95% CI. The I2 index was used to evaluate inter-study heterogeneity, and significance was set at $p < 0.05$. The symmetry of the funnel plot indicates a relatively low publication bias.

Results

Research inclusion process

The databases included 4836 articles, of which 2862 were removed. Next, 842 articles were excluded after screening titles and abstracts, and 590 studies were not retrieved. In total, 542 studies were further evaluated, and 503 were excluded because they were non-RCTs and had incomplete data on renal parameters. Three studies that had Type 1DM were excluded. Finally, 24 clinical studies were included in the meta-analysis (Fig. 1).

Characteristics of clinical research

Data were collected from 24 RCTs involving 37,848 patients; of these,18,312 and 19,543 individuals were assigned to the experimental and control groups, respectively. The included trials were published between 2011 and 2024. The treatment duration in the two groups ranged from 5 weeks to 3.84 years. All the selected clinical trials were randomized double-minded or open-label. Almost all the included studies recruited patients with T2DM. Descriptions of the clinical trials are presented in Table 1.

Evaluation of treatment in clinical trials

All studies exhibited random sequence generation [14, 15, 23]- [44]. Meanwhile, one trial lacked information regarding allocation concealment [14]. Four studies were characterized by a risk of bias for blinding of personnel, participants, and outcome assessment [33, 34, 39, 43]. For the outcome data, three clinical trials showed incomplete outcome data [15, 29, 31]. Four clinical trials have a reported bias or other biases [25, 26, 34, 43]. The quality of bias estimation for the clinical trials is presented in supplementary Fig. S1.

Influence of GLP-1 RA on renal function parameters in T2DM

The data summarized that intervention with GLP-1 RA positively influenced serum creatinine levels (WMD=-0.10, 95%CI -0.19 to -0.01, $P < 0.05$, I2 = 33%; Fig. 2; eGFR(WMD = 0.54, 95% CI 0.19 to 0.90, $P < 0.05$, I2 = 0%; Fig. 3; UAE(WMD=-11.92, 95% CI −23.50 to -0.33, $P < 0.05$, I2 = 0%; Fig. 4; UACR(WMD: −1.01 mg/g, 95% CI: −1.68, -0.34, $P < 0.05$, I2 = 10%; Fig. 5).

In five RCTs, the GLP-1 group was administered exenatide, liraglutide, and dulaglutide, whereas the control group received a placebo, SGL-T2 inhibitors, and insulin. The follow-up was 12–52 weeks. The experimental and control group comprised 461 and 468 patients, respectively.

In 15 RCTS, the GLP-1 group received exenatide, liraglutide, semaglutide, dulalutide, and albiglutide, whereas the control group received placebo, SGL-T2 inhibitors, and insulin. The follow-up period was 5 weeks to 3.84 years. The experimental and the control groups comprised 9172 and 9259 patients, respectively.

In 4 RCTs, the GLP-1 group was administered exenatide and liraglutide, whereas the control group received a placebo, SGL-T2 inhibitors, and insulin. The follow-up period was 16–48 weeks. The experimental and the control groups comprised 134 and 131 patients, respectively.

In eight RCTs, the GLP-1 group received exenatide, semaglutide liraglutide, and lixisenatide, whereas the control group received placebo, SGL-T2 inhibitors, and insulin. The follow-up period ranged from 14 weeks to 24 months. The experimental and control groups comprised 9162 and 9264 patients, respectively.

Publication bias

In this paper, the publication bias of the data is analyzed in the form of a funnel plot. Considering that Cr and UAE included too few data, the symmetry of the funnel plot was difficult to assess.Only eGFR and UACR were evaluated for publication bias.

Funnel plots show an asymmetry in eGFR (Supplementary Fig. S2)and UACR(Supplementary Fig. S3).

Discussion

Clinical trials have shown that liraglutide improves heart and kidney outcomes and reduces cardiovascular events and all-cause mortality in patients with T2DM [45]. In diabetes treatment, SGLT2i and GLP-1RAs the leading drugs for improving cardiovascular and kidney outcomes. The results of the EMPA-REG OUTCOME trial suggest the T2DM drug engaglipzin (SGLT2i) is beneficial for heart failure and kidney disease [46]. In the CREDENCE and AWARD-7 trials, the regression of UACR was approximately 35% and 23%, with the application of canagliflozin and daglipzin, respectively [14, 47]. Even in patients with T2DM with eGFR ≤ 30, the regression of UACR was approximately 65% with a combination of SGLT-2 inhibitor and GLP-1 receptor agonist, compared to baseline [48].

Glucose control in multiple stages of DKD is the basic clinical benefit of GLP-1RA binding without increasing the risk of hypoglycemia, including weight reduction, which eventually reduces cardiovascular and kidney outcomes [49, 50].

Many cardiovascular outcomes studies on GLP-1RAs have regarded kidney disease outcomes as secondary

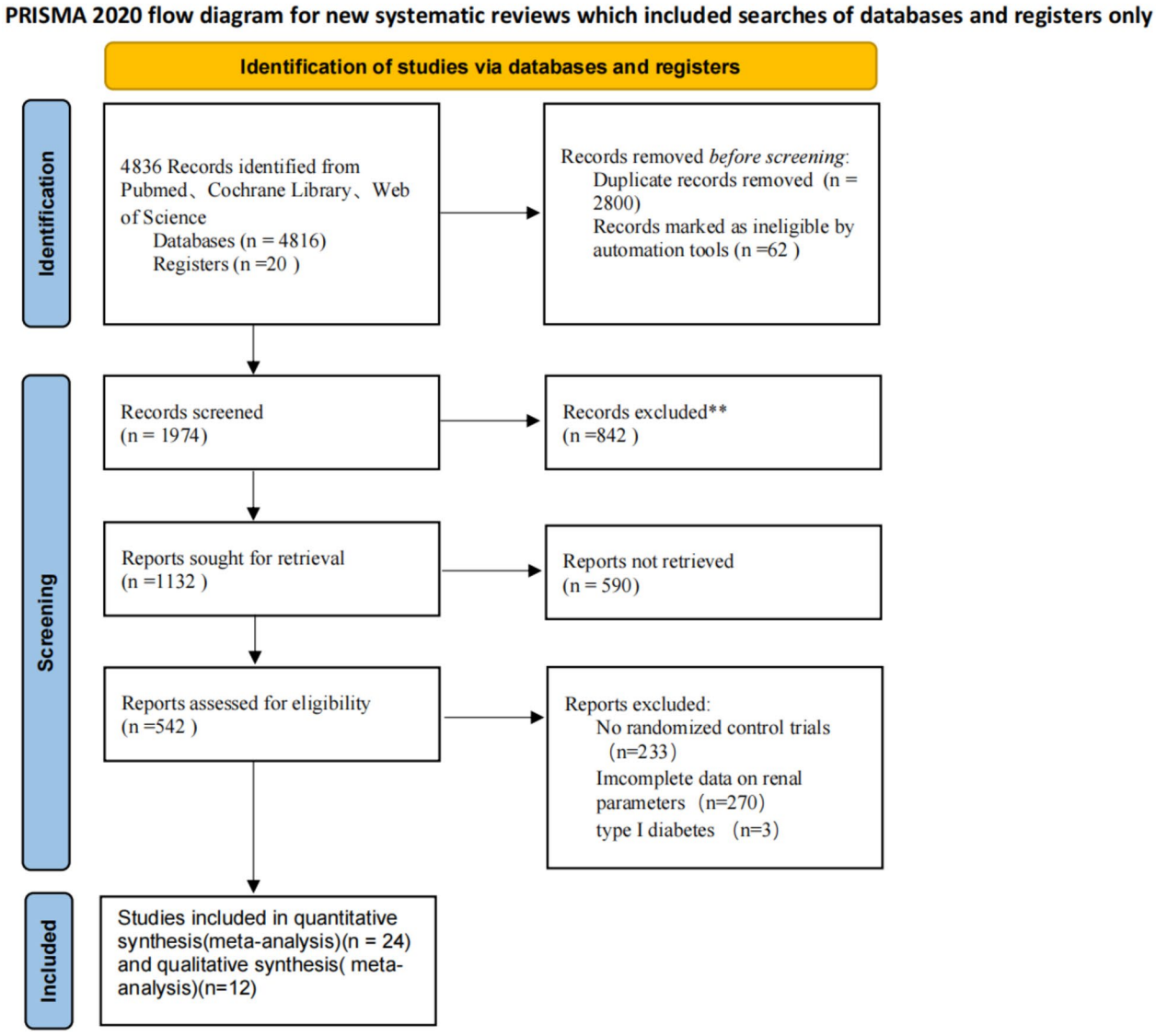

Fig. 1 Identification of studies via databases and registers

endpoints, and recent evidence indicates that GLP-1RAs have significant benefits for renal function. The SELECT study has indicated that among individuals with overweight or obese people without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing primary cardiovascular composite endpoint by 20% and nephropathy composite endpoint by 22% [51]. In particular, a reduced onset and progression of macroproteinuria and a slower rate of eGFR decline have been reported. Tuttle et al. [52]performed

Table 1 The characteristics of included studies

Author	Treatment duration	*n*	Study groups	Female (*n*, %)	Creatinine (mg/dL)	Glomerular filtration (ml/min/1.73 m2)	Urinary albumin excretion (mg/24 h)	Albumin-to-creatinine ratio (mg/g)
Pfeffer et al. 2015	24mouths	3034	Lixisenatide 20 μg/day	923 (30.4)	ND	ND	ND	10.0 [6.0, 28.0]
(ELIXA)		3034	Placebo	938 (30.9)	ND	ND	ND	10.4 [5.9, 32.6]
Derosa et al. 2013	48weeks	86	Exenatide 10 μg twice daily	43 (50)	ND	ND	98.2 ± 52.9	ND
		85	Placebo	44 (51)	ND	ND	93.6 ± 47.1	ND
von Scholten, MD et al.2017	28 weeks	27	Liraglutide 1.8 mg/day	5 (19)	ND	75 ± 23	183 (75–534)	ND
		27	Placebo	5 (16)	ND	73 ± 23	181 (84–353)	ND
Zhang et al.2011	16 weeks	13	Exenatide 10 μg twice daily	3 (23)	ND	ND	107 ± 71	ND
		18	Glimepiride 1–4 mg/day	5 (27)	ND	ND	111 ± 74	ND
Nakaguchi et, al.2020	24weeks	30	0.9 mg/day liraglutide	9(30)	0.92 ± 0.28	63.3 ± 18.9	ND	52.9 [15.7, 505.5]
		31	10 mg/day empagliflozin	10(33.3)	0.90 ± 0.32	67.1 ± 22.4	ND	66.6 [20.7, 134.2]
Tuttle.et, al2018		192	Dulaglutide 1·5 mg (*n* = 192	88 (46%)	1·86 ± 0·65	38·1 ± 13·2	ND	ND
(AWARD-7)	52weeks	190	Dulaglutide 0·75 mg (*n* = 190	86 (45%)	1·85 ± 0·63	38·3 ± 12·3	ND	ND
		194	Insulin glargine (*n* = 194)	101 (52%	1·82 ± 0·65	38.5 ± 13.0	ND	ND
Thomas Idorn, et al. 2016	12weeks	10	Control + liraglutide	3(30%)	0.71 ± 0.14	ND	ND	ND
		10	Control + placebo	2(20%)	0.69 ± 0.11	ND	ND	ND
Jiang et al. 2017	24weeks	77	liraglutide 1.8 mg	30(39%)	ND	80.83 ± 20.61	ND	ND
		79	dapagliflozin 10 mg	26(33%)	ND	81.51 ± 19.96	ND	ND
Mashayekhi et al. 2022	14weeks	44	liraglutide	31(70.5%)	ND	ND	ND	12.0 ± 23
		22	sitagliptin	15(68.2%)	ND	ND	ND	7.9 ± 7.6
		22	diet	14(63.8%)	ND	ND	ND	6.3 ± 3.8
Tuttolomondo et al. 2021	3months	56	conventional therapy + dulaglutide	32(57.2%)	ND	77.4 ± 11.2	ND	ND
		56	conventional therapy	35(62.5%)		76.1 ± 16.9	ND	ND
	9months	56	conventional therapy + dulaglutide	32(57.2%)	ND	77.4 ± 11.2	ND	ND
		56	conventional therapy	35(62.5%)		76.1 ± 16.9	ND	ND
Vanita et al. 2017	30weeks	362	semaglutide 0.5 mg	165(46%)	ND	97.9 ± 25.9	ND	ND
		360	semaglutide 1.0 mg	178(49%)	ND	98.0 ± 27.5	ND	ND
		360	insulin glargine	165(46%)	ND	99.7 ± 26.5	ND	ND
Hernandez et al2018(Harmony Outcomes)	28months	4731	Albiglutide	1427(30%)	ND	79.1 ± 25.6	ND	ND
		4732	Placebo	1467(31%)	ND	78.9 ± 25.4	ND	ND
ofi Mosenzon et al. 2019	26weeks	163	Oral semaglutide	80(49%)	ND	47 ± 10	ND	19.2 ± 79.63
		161	Placebo	88(55%)	ND	48 ± 10	ND	14.1 ± 63.19
Suzuki, k, et al. 2014	6months	24	liraglutide 0.9 mg/day	ND	ND	73.2 ± 13.4	ND	ND
		16	sitagliptin, 50 mg/day	ND	ND	73.7 ± 12.6	ND	ND
LEADER 2022	3.84years	4512	liraglutide	ND	ND	ND	ND	ND
		4498	placebo	ND)	ND	ND	ND	ND
Diamant M, et al. 2014	30weeks	247	Exenatide	119(48%)	ND	ND	ND	14.08 ± 28.68
		263	Lispro	130(49%)	ND	ND	ND	12.32 ± 15.65
Armstrong, M et al. 2016	12weeks	7	1.8 mg liraglutide	ND	0.8 ± 0.05	ND	ND	ND
		7	placebo	ND	0.7 ± 0.06	ND	ND	ND
Kuchay M, et al. 2020	24weeks	32	Dulaglutide	9(28)	0.84 ± 0.25	ND	ND	ND
		32	Control	10(31)	0.78 ± 0.15	ND	ND	ND
Art and Beek et al. 2020	26/28weeks	194	exenatide once weekly	76(39.2)	ND	ND	ND	68.2 ± 727
		274	comparators	90(32.8)	ND	ND	ND	72.2 ± 1045

Table 1 (continued)

Author	Treatment duration	*n*	Study groups	Female (*n*, %)	Creatinine (mg/dL)	Glomerular filtration (ml/min/1.73 m2)	Urinary albumin excretion (mg/24 h)	Albumin-to-creatinine ratio (mg/g)
Liakos et al2018	5 weeks	31	Liraglutide 1.2 mg/day	12 (38.7)	ND	82.3 ± 30.3	ND	ND
		31	placebo	9 (29)	ND	75.0 ± 21.2	ND	ND
Chen et, al.2017	26weeks	11	Exenatide	ND	ND	90 ± 35	ND	6.16(3.52,11.44)
		12	Insulin glargine	ND	ND	82 ± 22	ND	13.2(6.16,29.04)
Gullaksen, S et al. 2023	32weeks	20	Semaglutide	3(15)	ND	87 ± 21	ND	24.90 ± 55.99
		20	Placebo	6(30)	ND	91 ± 22	ND	13.90 ± 66.26
Rodbard, H,W et al. 2019	52weeks	412	oral semaglutide 14 mg	205 ± 49.9	ND	96 ± 15	ND	ND
		410	empagliflozin 25 mg	201 ± 49.0	ND	95 ± 15	ND	ND
SUSTAIN 6	2.1years	825	Semaglutide 0.5 mg	ND	ND	ND	ND	ND
		1648	Placebo	ND	ND	ND	ND	ND
		821	Semaglutide 1.0 mg	ND	ND	ND	ND	ND
		1648	Placebo	ND	ND	ND	ND	ND
FLOW	3.4years	1767	Semaglutide	519(29.4)	ND	46.9 ± 15.6	ND	ND
		1766	Placebo	550(31.1)	ND	47.1 ± 14.7	ND	ND

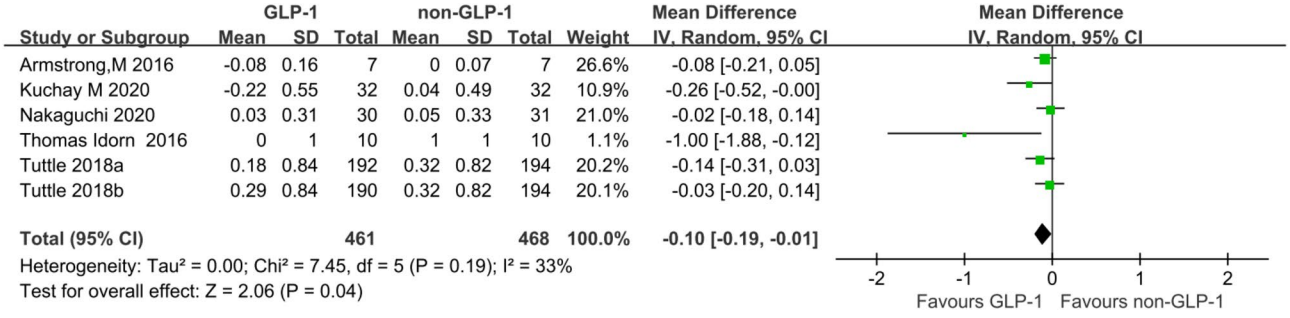

Fig. 2 Forest plot showing the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on creatinine levels in terms of the weighted mean difference and 95% fiducial intervals

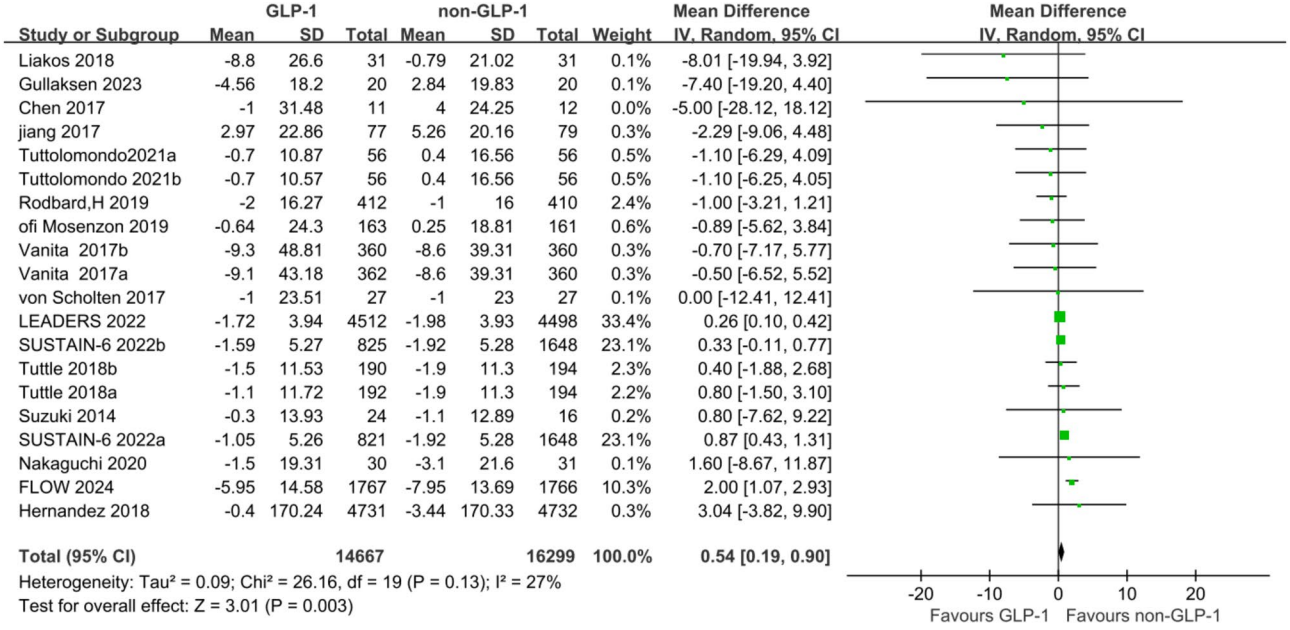

Fig. 3 Forest plot showing the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on glomerular filtration in terms of the weighted mean difference and 95% fiducial intervals

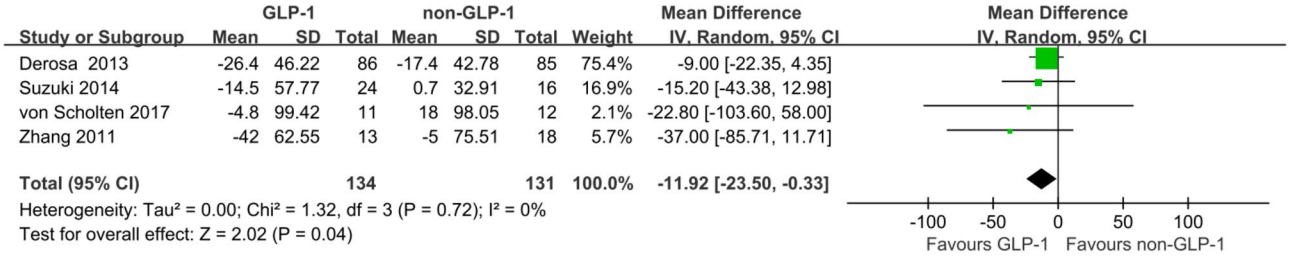

Fig. 4 Forest plot showing the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on urinary albumin excretion in terms of the weighted mean difference and 95% fiducial intervals

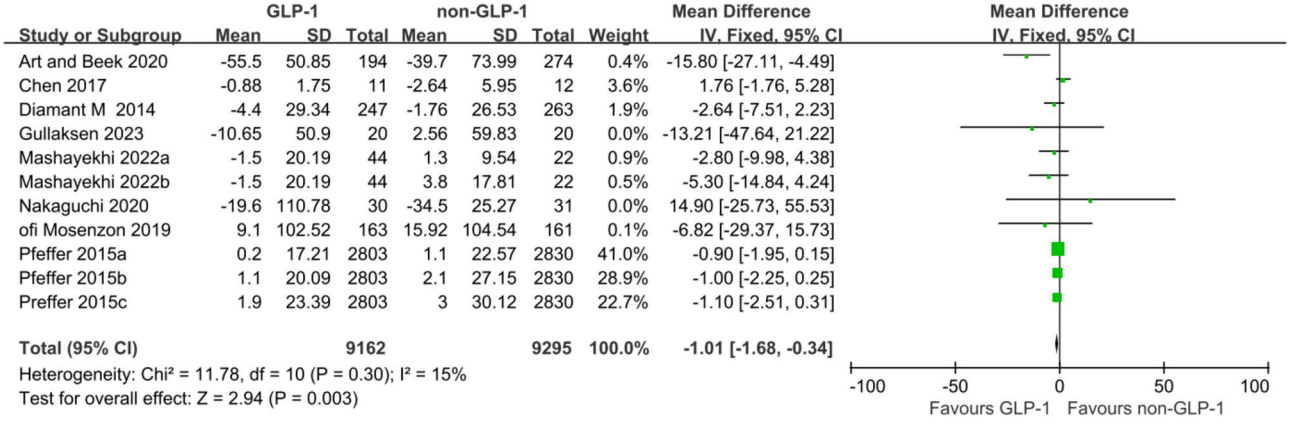

Fig. 5 Forest plot showing the effect of glucagon-like peptide-1 (GLP-1) receptor agonists on urinary albumin-to-creatinine ratio in terms of the weighted mean difference and 95% fiducial intervals

a post-hoc analysis of the SUSTAIN6 and PIONEER 6 trials and analyzed the effects of semaglutide versus placebo on eGFR decline. Estimated treatment differences in the general population semaglutide vs. placebo had a significant annual eGFR slope of 0.59(95% CI 0.29–0.89). The HR(semaglutide vs. placebo) for the duration of sustained eGFR decline across all eGFR thresholds in the general population was significantly < 1.0; Values for baseline eGFR (30–60 mL/ min/1.73 m2 were lower in the subgroup than the general population, although no significant connection between subgroups was observed for treatment effects. In exploratory analyses of the AWARD-7 [14] and REWIND trials [53], the dulaglutide group showed a slower decline than the basal insulin group.

Considering that human blood pressure is an important factor influencing eGFR, blood pressure by GLP- 1RAs may greatly influences eGFR. Mediated analysis results from the SUSTAIN 6 and LEADER datasets [54] suggest that HBA1c and systolic blood pressure (SBP) may partially account for the influence of semaglutide and liraglutide on the kidney, associated with established renal disease endpoints. GLP-1 RAs decrease SBP in individuals with T2DM and sharply reduce the circulating concentration of the vasoconstrictor angiotensin II (Ang II) [55]. Liraglutide significantly upregulated MAS1 in the glomeruli. The protein MAS1 encodes a signal receptor for angiotensin 1–7 (Ang1-7), which obeys a counter-regulatory pathway within the RAS, opposite to the vasoconstricting peptide, angiotensin II [56]. In a study on the effect of liraglutide on rat renal function [57], ACE2 was upregulated after the application of liraglutide, and ACE2 degraded AngI 1–9 and Ang II into Ang1-7, which plays a vasodilatory role by interacting with MAS receptors. Simultaneously, this was accompanied by the upregulation of glomerular MAS1, suggesting that liraglutide may affect renal hemodynamics by counteracting the effects of AngII. The regulation of urinary sodium and diuresis is also an important mechanism underlying the regulation of blood volume by GLP-1 RAs. GLP-1R-mediated natriuresis and diuresis may involve the inhibition of NHE3, which is located at the brush border of the renal proximal tubule [58]. Pharmacological doses of GLP-1 or GLP-1R agonists increase the phosphorylation of NHE3 at the PKA consensus sites Ser552 and Ser605 [59]. Decreasing both NHE3 surface distribution and Na+/K + ATPase activity is known as pressure natriuresis [60].In addition to direct natriuretic effects, GLP-1 RAs regulate the GLP-1 RA-ANP axis to play an indirect natriuretic role [61]. The effect of GLP-1RAs on renal function is multifaceted, and hemodynamic changes are not the only

factors affecting eGFR, which still needs to be confirmed in large clinical trials and animal tests.

Mann et al. [62] performed SUSTAIN 1–7 clinical trials and evaluated the renal function parameters of subcutaneous once-weekly semaglutide. Reductions in UACR were observed across the SUSTAIN 1–6 studies with semaglutide treatment and relevant comparators, whereas UACR was enhanced in the placebo groups. The positive influence of semaglutide on renal protection has been associated with reduced urine protein levels. In clinical trials related to the GLP-1 RAS, liraglutide (LEADER trial [63]) and duraglutide (REWIND trial [53]) were associated with a reduced risk of renal events, and a decrease in proteinuria played an important role in delaying renal deterioration.

Zhang et al. [64] analyzed the effects of metformin and liraglutide on urea and creatinine levels in 88 patients with diabetic nephropathy. The results manifest that the metformin group has a more significant effect than the liraglutide group (UAE ([51.83 mg/dL ± 12.43]) and creatinine [0.82 ± 0.19]versus UAE [73.63 mg/dL ± 17.59] and creatinine [1.01 mg/dL ± 0.26]($p < 0.0001$). A recent meta-analysis including 12,064 GLP-1 RA users and 10,712 nonusers elaborated on the effect of GLP-1 RAs on the doubling of serum creatinine levels. The users of GLP-1RAs did not affect their serum creatinine levels compared with the control.(relative risk,0.97[95%CI 0.78–1.21], $P = 0.79$) [65]. In the LEADERS trial's description of renal outcome endpoints, persistent doubling of serum creatinine levels has no significant difference between liraglutide and placebo (HR 0.89 (95% CI, 0.67–1.19, $P = 0.04$) [63].

In human kidneys, GLP-1 RA settles in proximal renal tubule cells and preglomerular vascular smooth muscle cells [66]. In previous animal models of atherosclerosis, semaglutide was proposed to control multiple inflammatory genes [67]. Stimulation of the GLP-1 receptor can directly reduces glomerular superoxide and renal NADPH oxidase levels by activating cAMP and PKA [68].GLP-1 RA also helps decrease the RAGE-mediated generation of reactive oxygen species, reducing oxidative stress in the kidneys [69]. Recent studies have shown that GLP-1 RAs can inhibit the NF-κB mediated inflammatory signaling pathway in adipose tissue of diabetic mice, leading to the reduction of peripheral adipose tissue inflammation [67]. Simulaneously, GLP-1 receptor agonists can modulate the MAPK pathway to inhibit inflammation [70], Instead of inhibiting autophagy and apoptosis [71]. The anti-albuminuric effects of GLP-1 RAs may have contributed to the preservation of renal function.Published mediation analyses of cardiovascular or renal outcomes may be partially mediated by eGFR, blood pressure, low-density lipoprotein cholesterol levels, and UACR, which corresponds with our meta-analysis.

This study is limited by its short follow-up period. The literature search only covered databases such as PubMed and Web of Science, and did not include conference abstracts or dissertations. This might lead to selection bias. Due to the limitation of the search scope, only English-language literature was included, which might result in the omission of unpublished grey literature and lead to overestimation or underestimation of the true effect size. Considering the small number of available trials, we were unable to analyze multiple factors or perform subgroup analyses to explore the changes in treatment effectiveness. Large RCTs on GLP-1 that specifically target renal function outcomes are lacking. Meanwhile, the strengths of our trial include the high adherence and retention rates. We included enomerous RCTs, and the trial data included many well-known studies, such as the Leaders, Sustain-6, AWARD-7, PIONEER 2, PIONEER 5, SUSTAIN 4, Harmony Outcomes, and Flow clinical trails. The benefits of GLP-1 agonists on complex renal outcomes are prominent, especially eGFR and UCAR.In clinical practice, for patients with diabetic nephropathy, GLP-1 receptor agonists can control blood sugar levels and at the same time, to some extent delay the deterioration of renal function. Therefore, they are highly recommended as the first choice. However, the clinical use of GLP-1 receptor agonists in patients with kidney disease or T2DM require further investigation.

Conclusion

GLP-1 RA treatment has a precise effect on renal function. Specific aspects included Cr levels, eGFR, UAE, and UACR. Owing to the study's limitations, additional research is essential to confirm the potential nephroprotective effects of GLP-1 RA.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01948-7.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

The authors have no acknowledgments to report.

Author contributions

Daqing Zhang designed the study and supervised the overall project. Wenjing Li drafted the article and critical revision. Na Sun collected data; Xiaoyan Liang participated in data analysis.

Funding

This job was supported by a grant from the Shandong Province Medical Workers Science and Technology Innovation Program (SDYWZGKCJH2023026), Scientific Research Foundation of Binzhou People's Hospital (XJ2023006307), Shandong Province Medical and Health Development Program (202301030188).

Data availability
The data of this study can be obtained from the corresponding author according to reasonable requirements.

Declarations

Ethics approval and consent to participate
This is a systematic review and meta-analysis, ethics approval and consent to participate are not applicable.

Consent for publication
Not applicable. This study does not involve human participants.

Competing interests
The authors declare no competing interests.

Received: 17 May 2024 / Accepted: 28 April 2025
Published online: 07 May 2025

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