

Meta-analysis of the efficacy of liraglutide in patients with type 2 diabetes accompanied by incipient nephropathy

WEI LIU¹, JIANGYI YU^{1,2}, TING TIAN^{1,2}, JUNJUN MIAO² and WENBIN SHANG¹

¹Department of Endocrinology and Metabolism, Affiliated Hospital of Nanjing University of Chinese Medicine;

²Department of Endocrinology and Metabolism, Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing, Jiangsu 210029, P.R. China

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Abstract. The efficacy of liraglutide in patients with type 2 diabetes accompanied by early-stage nephropathy has remained to be fully elucidated. The present meta-analysis was performed to determine the clinical outcomes associated with liraglutide treatment. The PubMed, Ovid, Cochrane Library, Chinese National Knowledge Infrastructure and Wanfang databases were searched in October 2018 to identify randomized controlled trials of liraglutide for diabetes patients with early-stage nephropathy. The treatment effect was estimated by calculating the mean difference (MD). Heterogeneity was assessed using χ^2 and I^2 tests. In addition, risk of bias graphs and summaries were used to assess the quality of the trials included. A total of 13 randomized controlled trials were included in the present meta-analysis. In subjects with stage I-II diabetic nephropathy (DN), liraglutide had obvious advantages in lowering the urinary albumin-to-creatinine ratio [UACR; MD=-90.96, 95% confidence interval (CI)=-94.12 to -87.80, $P<0.00001$], urinary albumin excretion rate (UAER; MD=-64.86, 95% CI=-66.63 to -63.08, $P<0.00001$), serum creatinine (Scr; MD=-13.67, 95% CI=-17.88 to -9.46, $P<0.00001$). In subjects with stage-III DN, liraglutide had favorable effects on renal function

(UACR: MD=-11.23, 95% CI=-13.14 to -9.32, $P<0.00001$; UAER: MD=-14.06; 95% CI=-6.93 to -11.18; $P<0.00001$; Scr: MD=-9.17, 95% CI=-14.61 to -3.72, $P=0.0010$) and exhibited anti-inflammatory effects (transforming growth factor- β 1: $P<0.00001$; tumor necrosis factor- α : $P=0.006$; interleukin-6: $P<0.00001$). Furthermore, liraglutide also reduced the blood lipid levels, body mass index and post-prandial blood glucose. The most common adverse effects of liraglutide were gastrointestinal tract reactions and hypoglycemia, but these symptoms resolved quickly. Liraglutide appears to be effective in reducing proteinuria, improving renal function, producing an anti-inflammatory effect and ameliorating glucose and lipid metabolism in diabetic patients with early-stage nephropathy.

Introduction

Diabetes mellitus (DM) has reached endemic levels, with its worldwide prevalence estimated to increase to 552 million by 2030 (1). Among the major burdens of diabetes patients are microvascular and macrovascular complications, particularly diabetic nephropathy (DN). DN is functionally characterized by initial glomerular hyperfiltration and persistent albuminuria, followed by a progressive decline in the glomerular filtration rate (GFR), leading to the development of end-stage renal disease (ESRD).

The major treatment for DN is tight control of blood glucose and blood pressure, but these methods do not slow down the progression of DN to ESRD. Renal replacement therapy is inevitable once DN has progressed to ESRD, but the medical cost of renal replacement is high; thus, treatment should be provided during the early stages of DN. The urinary albumin-to-creatinine ratio (UACR) and estimated (e)GFR are used for screening for incipient DN. Furthermore, five distinct stages of chronic kidney disease have been defined based on the progression of renal impairment (2). In general, stages I-III are classified as early-stage DN, stage IV as intermediate-stage (moderate DN) and stage V as late-stage/severe DN, with an eGFR of ≤ 30 ml/min/1.73 m² and persistent macroalbuminuria (UACR ≥ 300 mg/g).

Traditional glucose-lowering treatments include insulin, metformin, sulfonylureas, meglitinides and thiazolidinediones. Although these drugs are effective in reducing the risk of diabetic complications, they are associated with significant

Correspondence to: Professor Jiangyi Yu, Department of Endocrinology and Metabolism, Jiangsu Province Hospital of Traditional Chinese Medicine, 155 Han-Zhong Road, Nanjing, Jiangsu 210029, P.R. China
E-mail: yujiangyi2017@163.com

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DN, diabetic nephropathy; ESRD, end-stage renal disease; FBG, fasting blood glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; IL-6, interleukin-6; MD, mean difference; PBG, post-prandial blood glucose; Scr, serum creatinine; TC, total cholesterol; TNF- α , tumor necrosis factor- α ; TGF- β 1, transforming growth factor- β 1; UAER, urinary albumin excretion rate; UACR, urinary albumin-to-creatinine ratio

Key words: liraglutide, type 2 incipient diabetic nephropathy, meta-analysis

side effects, including hypoglycemia and weight gain. Over the last decade, several novel glucose-lowering drugs have been introduced and have been increasingly used as treatments for diabetes and its complications. Glucagon-like peptide-1 (GLP-1) receptor agonists are among these more recent drug classes.

GLP-1 receptor agonists are a class of anti-hyperglycemic drugs for type 2 diabetes. They include exenatide, lixisenatide, liraglutide, dulaglutide and albiglutide. Liraglutide was the second GLP-1 receptor agonist to receive regulatory approval by the Food and Drug Administration for type 2 diabetes in January 2010 (3). However, whether liraglutide offers therapeutic advantages compared with other drugs for DN has remained to be confirmed. Recently, Mann *et al* (4) performed a randomized controlled trial to evaluate the change of renal outcomes of treatment with liraglutide. 9,340 DN patients were assigned to receive liraglutide or placebo, which results suggested that the liraglutide group had fewer patients who exhibited persistent macroalbuminuria when compared with the placebo group. That is to say, liraglutide may decrease persistent macroalbuminuria and improve renal outcomes. By contrast, the study by Davies *et al* (5) was conducted to establish the efficacy and safety of liraglutide. A total of 279 patients with moderate DN were divided into liraglutide and placebo groups, and the results demonstrated that no changes in renal function were observed in the liraglutide and placebo groups. The aforementioned two studies had certain limitations: First, although the study of Mann *et al* (4) covered early-stage, moderate and late-stage DN patients, it did not particularly proceed subgroup analyses. In other words, the result showed that liraglutide lowered the level of proteinuria and improved renal function, but it did not clarify which stage of DN was affected by liraglutide. Second, the study by Davies *et al* (5) only showed that liraglutide had no effect on moderate DN, but it did not clarify whether liraglutide had therapeutic effects on DN in other stages, such as the early stage. Therefore, the effects of liraglutide against incipient DN were not determined in these studies. The present study was the first analysis investigating the effect of liraglutide in patients with type 2 diabetes who also had incipient DN. Of note, it was indicated that liraglutide has renoprotective effects in patients with early-stage DN.

Materials and methods

Search strategy. The PubMed, OVID, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI) and WanFang databases were searched by two investigators independently. These databases were extensively searched and articles from the time the databases were established until October 2018 were examined. The following search terms were used: ('liraglutide') and ('diabetic nephropathies' or 'diabetic nephropathy' or 'diabetic kidney diseases' or 'diabetic complications'). The publications were first filtered based on title, abstract and key words, and the full-text versions were then assessed while applying the inclusion and exclusion criteria (described below). The publication language was restricted to English and Chinese.

Selection criteria. All relevant articles focusing on the association between liraglutide and renal function index were

collected. The following studies were included: a) Studies performed as randomized controlled trials; b) studies that involved type 2 diabetes patients with stage I-III nephropathy: Stages I and II were defined by an eGFR of ≥ 60 ml/min/1.73 m² with normal and mildly increased albuminuria (UACR < 30 mg/g), respectively, while stage III was defined by an eGFR of 30-60 ml/min/1.73 m² and an increase in UACR from 30 to 300 mg/g in two morning spot urine collections sustained over 12 weeks (2); c) studies that included patients who were under a controlled diet and exercise therapy, treatment with anti-hypertensive drugs or other anti-hyperglycemic treatments (control group), and those treated with liraglutide (experimental group); d) studies that reported on renal function outcomes, including UACR, urinary albumin excretion rate (UAER), serum creatinine (Scr); and e) studies with a duration of >8 weeks. The following studies were excluded: a) Those that included no information on renal function or the biochemical index of type 2 DN; b) those with duplicate clinical data published by the same authors but in different periodicals; c) those with unclear or inappropriate diagnostic criteria, intervention measures or outcome indicators; d) case reports, letters, reviews, expert opinion, conference abstracts, editorials, and studies published in a language other than English or Chinese; and e) articles using cell lines and/or *in vitro*/*ex vivo* studies.

Data extraction. Data included in the present study were extracted independently by authors JY and JM. If disagreement was encountered, the third author (TT) was consulted for consensus. The general information, including the name of the first author, the year of publication, type of trial, number of patients, the treatment methods, course of treatment and outcome data were extracted from each of the included papers. Study characteristics and clinical examination data were generalized and are described in table format.

Statistical analysis. RevMan 5.3 software was downloaded from the Cochrane Collaboration website and used for meta-analysis. Clinical heterogeneity and methodological heterogeneity of the included studies were analyzed using the χ^2 and I^2 tests, respectively. If acceptable statistical heterogeneity existed among the studies ($P > 0.1$ and $I^2 < 50\%$), the fixed-effect method was used to pool the data (6). Otherwise, the random-effects model was used (6,7). The mean difference (MD) and 95% confidence intervals (CIs) were used to compare continuous variables, while risk ratios and 95% CIs were used to compare dichotomous variables (7). Whenever heterogeneity was significant, it was attempted to determine its source using the study-by-study exclusion method. $P < 0.05$ was considered to indicate statistical significance. Egger's test performed using Stata 12.0 software (Stata Corp) and funnel plots drawn with RevMan 5.3 software were used to detect publication bias.

Assessment of quality of evidence. The risk of bias was assessed by two investigators independently, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (7). Disagreements were resolved by a third reviewer. The quality appraisal of the literature

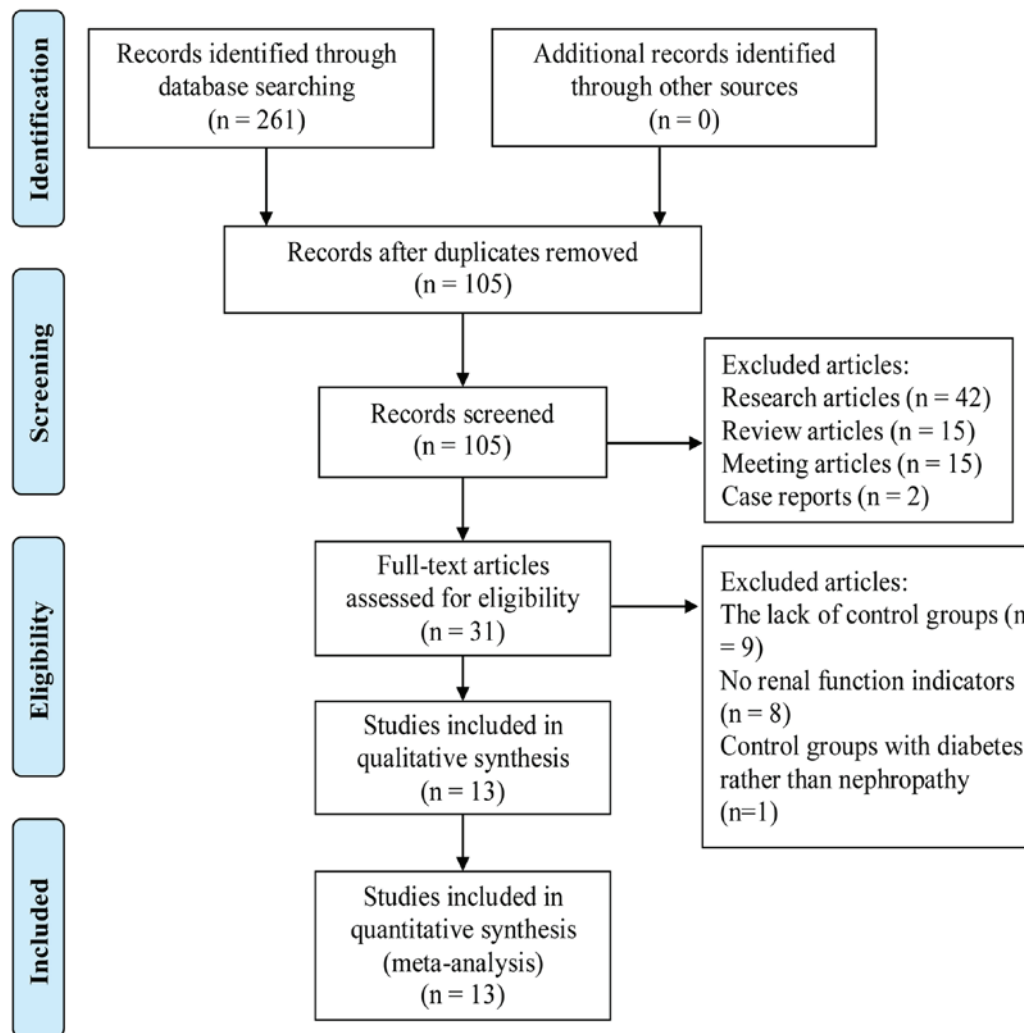


Figure 1. PRISMA flow diagram of study selection.

included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Articles that had clearly described details and met or surpassed the quality criteria were defined as low-risk; otherwise, they were deemed high-risk. Equivocal articles in terms of quality criteria were deemed to be of unclear risk.

Results

Literature search and selection. Initially, 261 relevant records were retrieved from the PubMed, Ovid, Cochrane Library, CNKI and WanFang databases. A total of 31 full-text articles were then extracted for detailed assessment and were filtered via their titles and abstracts for eligibility assessment for final inclusion. Following exclusion of 9 crossover trials without control groups, as well as 8 trials that lacked renal function marker analysis, one study of which had a control group of patients with DM rather than DN, 13 publications that satisfied the inclusion criteria were finally selected for inclusion in the meta-analysis (8-20). The article search and study selection process are displayed in Fig. 1.

Study characteristics. Of the total 1,187 patients included, 590 belonged to the treatment group, while 597 belonged to the control group and received routine treatment, including a controlled diet and exercise therapy, anti-hypertensive drugs or other anti-hyperglycemic treatments. The treatment group received liraglutide combined with routine treatment, anti-hypertensive drugs or other anti-hyperglycemic treatment. The doses of liraglutide used in the trials included were largely consistent. Subcutaneous injection of liraglutide was administered prior to bedtime on a daily basis. The initial dose in the first week was 0.6 mg/day and was increased from 1 to 1.2 mg/day in the second week. Among the 13 trials, 12 adopted a two-armed parallel group design, while one [Zhang *et al* (8)] adopted a three-armed group design. The durations of interventions varied among the diabetes trials, ranging from 8 to 24 weeks. A total of 7 studies lasted for 24 weeks, 3 lasted for 8 weeks, 1 lasted for 10 weeks and the remaining ones lasted for 12 weeks. Basic information about the studies included are presented in Table I.

Risk of bias. The risk of bias assessments is presented in Fig. 2. All trials were randomly designed, but four (9,13,18,19) were judged to have unclear risk of bias owing to allocation concealment.

Table I. Characteristics of the studies included.

First author (year)	Sample cases	Testing scheme	Test group	Control group	Duration (weeks)	Outcomes	(Refs.)
Zhang (2017)	22/20	RCT	LIR (0.6 to 1.2 mg qd) plus RT	RT	10	ACIKLM	(8)
Zha (2018)	30/30	RCT	LIR (0.6 to 1.2 mg qd) plus Huang kui capsule	Huang kui capsule (2.5 g tid)	24	ADGH	(9)
Dong (2018)	43/43	RCT	LIR (0.6 to 1.2 mg qd) plus INS	INS	24	BDGHI	(10)
Li (2017)	21/22	RCT	LIR (0.6 to 1.2 mg qd) plus RT	RT	12	ABCDEFI	(11)
Zheng (2015)	110/110	RCT	LIR (0.6 to 1.2 mg qd) plus INS	INS	8	ADFH	(12)
Yan (2016)	100/100	UNK	LIR (0.6 to 1.2 mg qd) plus TEL	TEL	10	CIKLM	(13)
Shen (2017)	30/30	RCT	LIR (0.6 to 1.2 mg qd) plus OLM and INS	OLM (20 mg qd) plus INS	24	ACEFG	(14)
Chen (2016)	30/31	RCT	LIR (0.6 to 1.2 mg qd) plus RT	RT	24	ACDEFI	(15)
Ren (2015)	24/24	RCT	LIR (0.6 to 1.2 mg qd) plus INS	INS	24	ACDGI	(16)
Zhao (2014)	19/26	UNK	LIR (0.6 to 1.2 mg qd) plus VAL	VAL	24	CDJ	(17)
Aiyitan (2017)	89/73	UNK	LIR (0.6 to 1.2 mg qd) plus INS	INS	8	BGH	(18)
Liu (2016)	59/75	RCT	LIR (0.6 to 1.2 mg qd) plus INS	INS	8	BGH	(19)
Liu (2015)	13/13	RCT	LIR (0.6 to 1.2 mg qd) plus OLM and INS	OLM (20 mg qd) plus INS	24	DGJ	(20)

RCT, randomized controlled trial; UNK, unknown; qd, once a day; LIR, liraglutide; RT, routine treatment; VAL, valsartan; INS, insulin; TEL, telmisartan; OLM, olmesartan; A, fasting blood glucose; B, post-prandial blood glucose; C, glycosylated hemoglobin; D, body mass index; E, total cholesterol; F, triglyceride; G, urine albumin-to-creatinine ratio; H, urine albumin excretion rate; I, serum creatinine; J, serum cystatin C; K, transforming growth factor- β 1; L, tumor necrosis factor; M, interleukin-6.

Blinding of participants and personnel was not performed in one study (17); furthermore, another study did not perform blinding of outcome assessors (18). In addition, four studies did not specify whether the participants and personnel were blinded (14,16,18,19), and four studies did not specify whether blinding of the outcome assessors was performed (12-14,17). Attrition bias was ambiguous in seven of the trials (9,12-14,17-19); however, most trials had a low risk of reporting bias or other biases, and only one had an unclear risk of reporting bias (8).

Effect of interventions

Effect on proteinuria and renal function. According to the stage of DN of the subjects, the 13 trials (8-20) were divided into two subgroups: Four trials (11,13,18,19) belonged to stages I and II, and the remaining ones belonged to stage III. In addition, UACR, UAER and Scr were evaluated to determine the effect of liraglutide on proteinuria and renal function.

A total of 2 trials (18,19) investigated the effect of liraglutide during DN stages I and II on the UACR and UAER. The treatment and control groups comprised 148 patients each. No significant heterogeneity was identified among the studies (UACR: $\chi^2=0.01$; $I^2=0\%$, $P=0.93$; UAER: $\chi^2=0.00$; $I^2=0\%$, $P=0.96$); hence, a fixed-effects model was used for the meta-analyses. The UACR and UAER were lower in the treatment group than those in the control group (UACR: MD=-90.96, 95% CI=-94.12 to -87.80, $P<0.00001$;

UAER: MD=-64.86, 95% CI=-66.63 to -63.08, $P<0.00001$; Fig. 3A and B). A total of 2 trials (11,13) were used to compare Scr levels between the two groups. The treatment group included 121 patients and the control group included 122 patients. No significant heterogeneity was identified between the two trials ($\chi^2=0.14$; $I^2=0\%$, $P=0.71$). Patients receiving liraglutide had better Scr levels than the subjects in the control group (MD=-13.67, 95% CI=-17.88 to -9.46, $P<0.00001$; Fig. 3C).

As for stage-III DN, 5 trials (9,10,14,16,20) reported on the UACR with 140 patients each in the treatment and control group. Without statistical heterogeneity among the studies ($\chi^2=7.08$; $I^2=43\%$, $P=0.13$), a fixed-effects model was selected for the pooled analysis, which revealed that the treatment group was better than the control group in terms of UACR (MD=-11.23, 95% CI=-13.14 to -9.32, $P<0.00001$; Fig. 4A). A total of 3 trials (9,10,12) compared the UAER between the treatment group and the control group (183 patients per group). No significant heterogeneity was observed ($\chi^2=3.28$; $I^2=39\%$, $P=0.19$) and a fixed-effects model was used for the pooled analysis. The treatment group had a lower UAER than the control group (MD=-14.06; 95% CI=-16.93 to -11.18; $P<0.00001$; Fig. 4B). Furthermore, analysis of 4 trials reporting on Scr levels (8,10,15,16) indicated that there was a significant difference in Scr levels between the treatment group ($n=119$) and control group ($n=118$). Heterogeneity testing again showed no statistically significant difference between these studies ($\chi^2=5.32$; $I^2=44\%$, $P=0.15$), and thus,

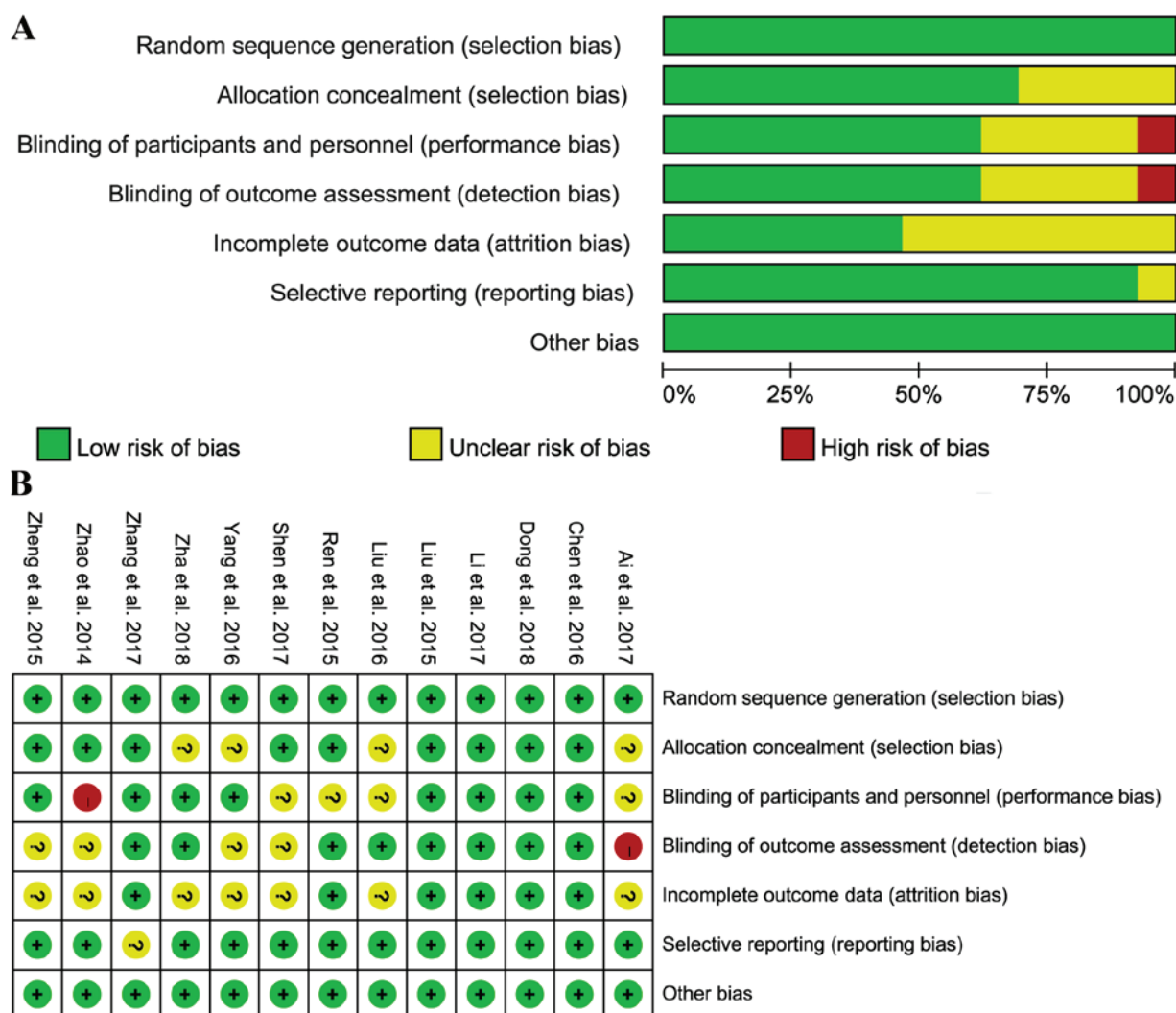


Figure 2. Risk of bias graphs and summaries in various categories across all of the studies included. (A) Risk of bias graph; (B) risk of bias summary.

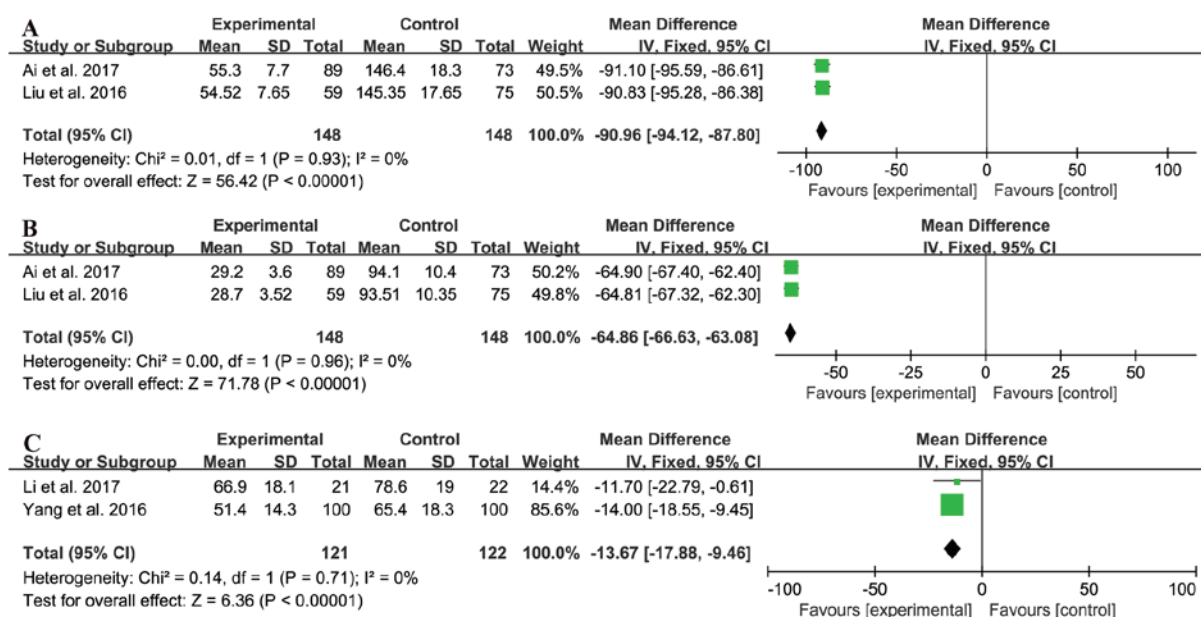


Figure 3. Forest plots for the effects of liraglutide in patients with stage I-II (eGFR ≥ 60 ml/min/1.73 m², UACR < 30 mg/g) diabetic nephropathy. (A) Urinary albumin-to-creatinine ratio; (B) urinary albumin excretion rate; (C) serum creatinine. SD, standard deviation; CI, confidence interval; IV, inverse variance; df, degrees of freedom; green squares, effect size of each study; size of green squares, weight of each study; Black diamonds, test for overall effect; horizontal lines, confidence intervals.

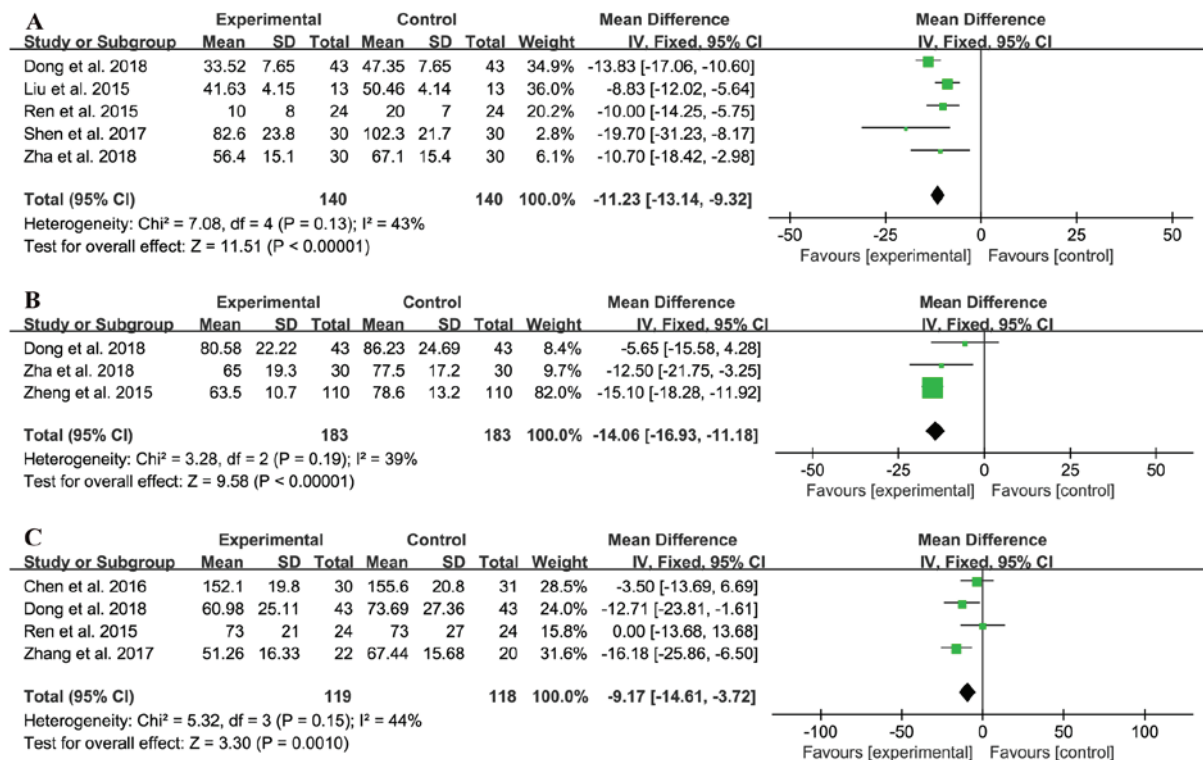


Figure 4. Forest plots for the effects of liraglutide treatment in patients with stage III ($30 \text{ ml/min/1.73 m}^2 < \text{eGFR} < 60 \text{ ml/min/1.73 m}^2$, $30 \text{ mg/g} < \text{UACR} < 300 \text{ mg/g}$) diabetic nephropathy. (A) Urinary albumin-to-creatinine ratio; (B) urinary albumin excretion rate; (C) serum creatinine. SD, standard deviation; CI, confidence interval; IV, inverse variance; df, degrees of freedom; green squares, effect size of each study; size of green squares, weight of each study; black diamonds, test for overall effect; horizontal lines, confidence intervals.

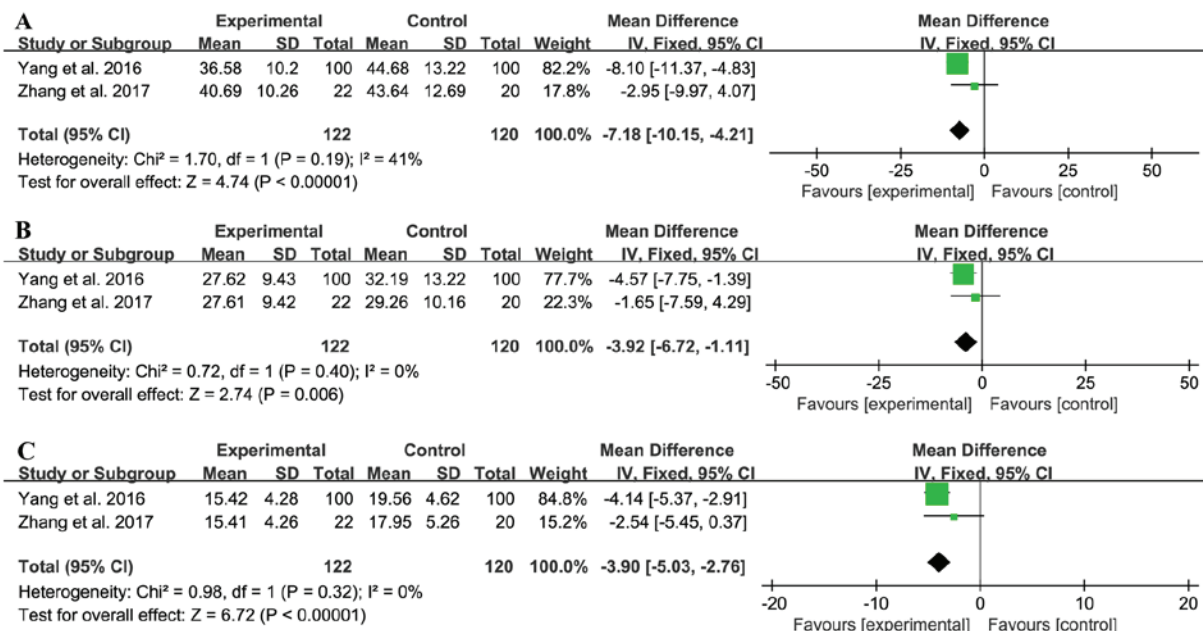


Figure 5. Forest plot for the anti-inflammatory effects of liraglutide treatment in early-stage diabetic nephropathy. (A) Transforming growth factor- β_1 ; (B) tumor necrosis factor- α ; (C) interleukin-6. SD, standard deviation; CI, confidence interval; IV, inverse variance; df, degrees of freedom; green squares, effect size of each study; size of green squares, weight of each study; black diamonds, test for overall effect; horizontal lines, confidence intervals.

the fixed-effects model was selected for pooled analysis, which revealed that the treatment group exhibited better Scr levels than the control group ($\text{MD} = -9.17$, 95% $\text{CI} = -14.61$ to -3.72 , $P = 0.001$; Fig. 4C). Overall, the results suggested that liraglutide ameliorates renal function.

Effect on inflammation. A total of 2 trials (8,13) compared transforming growth factor- β_1 (TGF- β_1), tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) levels between the treatment group ($n = 122$) and control group ($n = 120$). No significant heterogeneity was observed (TGF- β_1 : $\chi^2 = 1.70$;

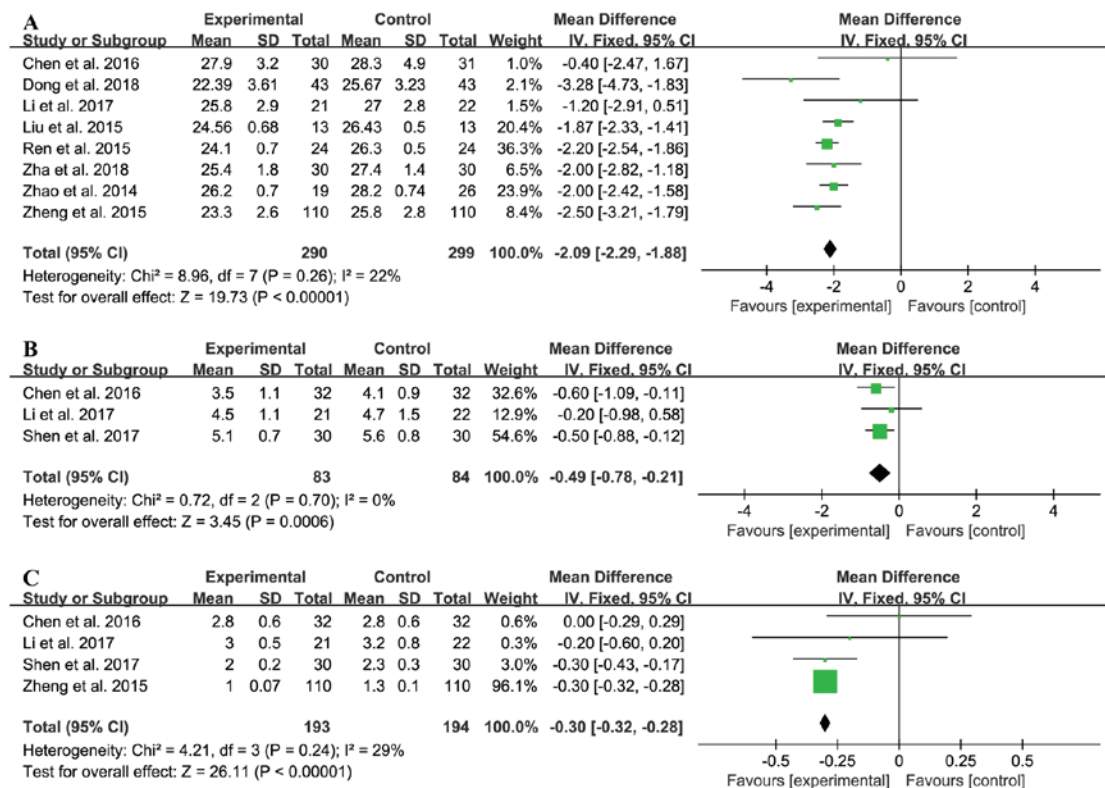


Figure 6. Forest plots for the effects of liraglutide on lipid metabolism of patients with diabetic nephropathy. (A) Body mass index; (B) total cholesterol; (C) triglyceride. SD, standard deviation; CI, confidence interval; IV, inverse variance; df, degrees of freedom; green squares, effect size of each study; size of green squares, weight of each study; black diamonds, test for overall effect; horizontal lines, confidence intervals.

$I^2=41\%$, $P=0.19$; TNF: $\chi^2=0.72$; $I^2=0\%$, $P=0.40$; IL-6: $\chi^2=0.98$; $I^2=0\%$, $P=0.32$), and a fixed-effects model was used for the pooled analyses. The treatment group had lower levels of the inflammatory factors compared with those in the control group (TGF- β_1 : MD=-7.18; 95% CI=-10.15 to -4.21; $P<0.00001$; TNF: MD=-3.92; 95% CI=-6.72 to -1.11; $P=0.006$; IL-6: MD=-3.90; 95% CI=-5.03 to -2.76; $P<0.00001$), indicating that liraglutide exhibited anti-inflammatory effects in patients with early-stage of DN (Fig. 5).

Effect on body mass index (BMI) and blood lipids. A total of 8 trials (9-12,15-17,20) reported on the BMI in the treatment group ($n=290$) and control group ($n=299$), and no significant heterogeneity was determined ($\chi^2=8.96$, $I^2=22\%$, $P=0.26$). The fixed-effects model was used for the pooled analysis, which indicated that liraglutide was associated with a reduced BMI (MD=-2.09, 95% CI=-2.29 to -1.88, $P<0.00001$; Fig. 6A). A total of 3 trials (11,14,15) compared the total cholesterol (TC) levels between the treatment group ($n=83$) and control group ($n=84$), and no significant heterogeneity was observed ($\chi^2=0.72$, $I^2=0\%$, $P=0.70$). A fixed-effects model was used for the meta-analysis, indicating that liraglutide treatment reduced the level of TC (MD=-0.49, 95% CI=-0.78 to -0.21, $P=0.0006$; Fig. 6B). Furthermore, 4 trials (11,12,14,15) compared the triglyceride (TG) levels between the treatment group ($n=193$) and control group ($n=194$), and no significant heterogeneity was determined ($\chi^2=4.21$, $I^2=29\%$, $P=0.24$). Therefore, the fixed-effects model was used for the meta-analysis, revealing that liraglutide also decreased the level of TG (MD=-0.30, 95% CI=-0.32 to -0.28, $P<0.00001$; Fig. 6C). These results

suggested that, compared with the control treatment, liraglutide lowers the blood lipid levels and the BMI.

Effect on blood glucose and glycosylated hemoglobin (HbA1c). A total of 7 trials (8,9,11,12,14-16) evaluated the effect of liraglutide on fasting blood glucose (FBG) levels in the treatment group ($n=267$) compared with control subjects ($n=267$). The statistical heterogeneity of the FBG data was acceptable ($\chi^2=4.72$; $I^2=0\%$, $P=0.58$); therefore, the fixed-effects model was used for meta-analysis. The pooled analysis indicated no difference between the treatment group and control group (MD=0.01; 95% CI=-0.15 to 0.16; $P=0.91$; Fig. 7A).

A total of 4 trials (10,11,18,19) investigated the effect of liraglutide on post-prandial blood glucose (PBG) levels. The liraglutide group comprised 212 patients, while the control group comprised 213 patients; moderate heterogeneity was observed ($\chi^2=6.06$; $I^2=50\%$, $P=0.11$) and a random-effects model was used for analysis. The results suggested that the treatment group had better PBG levels than the control group (MD=-1.51; 95% CI=-1.81 to -1.22; $P<0.00001$; Fig. 7B).

As presented in Fig. 7C, 7 trials (8,11,13-17) reported on the effect of liraglutide on HbA1c, and all studies had acceptable heterogeneity ($\chi^2=9.14$; $I^2=34\%$, $P=0.17$); therefore, the fixed-effects model was used. The meta-analysis indicated no significant difference between the treatment group and control group in terms of HbA1c levels (MD=-0.07; 95% CI=-0.15 to 0.01; $P=0.10$).

Adverse events. Only 5 trials (8,10,15-17) reported on adverse events, 3 of which (8,15,17) reported that no adverse events

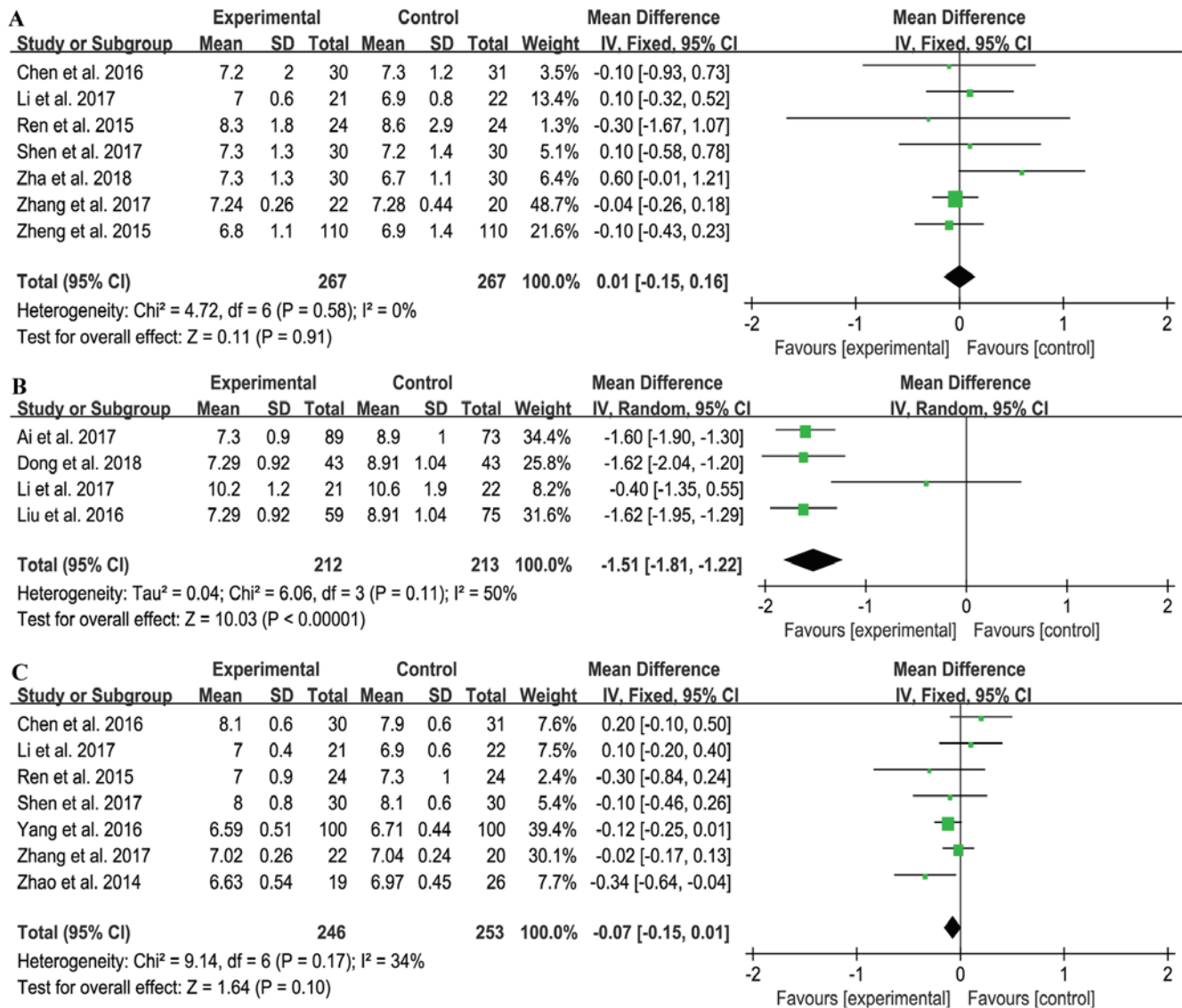


Figure 7. Forest plots for the effects of liraglutide in patients with early-stage diabetic nephropathy ($eGFR > 30$ ml/min/1.73 m^2 , $UACR < 300$ mg/g). (A) Fasting blood glucose; (B) postprandial blood glucose; (C) glycosylated hemoglobin A1c. SD, standard deviation; CI, confidence interval; IV, inverse variance; df, degrees of freedom; green squares, effect size of each study; size of green squares, weight of each study; black diamonds, test for overall effect; horizontal lines, confidence intervals.

occurred during the treatment period. Of the remaining 2 trials, 1 (10) indicated that patients in the treatment group presented with hypoglycemia ($n=1$), nausea ($n=5$) and diarrhea ($n=7$); however, the same adverse events were experienced in patients in the control groups ($n=7$, $n=7$ and $n=8$, respectively). The other trial (16) reported that 12.5% patients in the treatment group had exhibited gastrointestinal-tract reactions ($n=3$). However, there were no serious adverse events reported in any of these trials. The most common adverse events were gastrointestinal tract reactions and hypoglycemia, but they resolved quickly.

Evaluation of publication bias. In the present study, funnel plots and Egger's test were used to identify publication bias (Fig. 8A, BMI; Fig. 8B, FBG; Fig. 8C, HbA1c). Symmetry was observed in Fig. 8, and the values reported in one study were beyond the 95% CI range (Fig. 8B). However, those of the other trials were within the 95% CI range (Fig. 8A and C). At

the same time, Egger's test for BMI ($P=0.085$), FBG ($P=0.448$) and HbA1c ($P=0.709$) also suggested that there was no publication bias in the studies included.

Discussion

DN is one of the complications of DM. The pathogenesis of DN is linked to various factors, including metabolic and hemodynamic abnormalities (21). The primary treatment for DN is tight control of blood glucose and blood pressure, but these methods do not slow down the progression of DN. Over the last decade, liraglutide has been introduced and has been increasingly used for the treatment of DM and its complications.

Liraglutide is one of the representative GLP-1 receptor agonist drugs. Physiologically, GLP-1 exerts its actions through the GLP-1 receptor in pancreatic β -cells, resulting in glucose-dependent insulin secretion and thus reduction in blood glucose levels (22-24). However, only 10-15% of endogenously

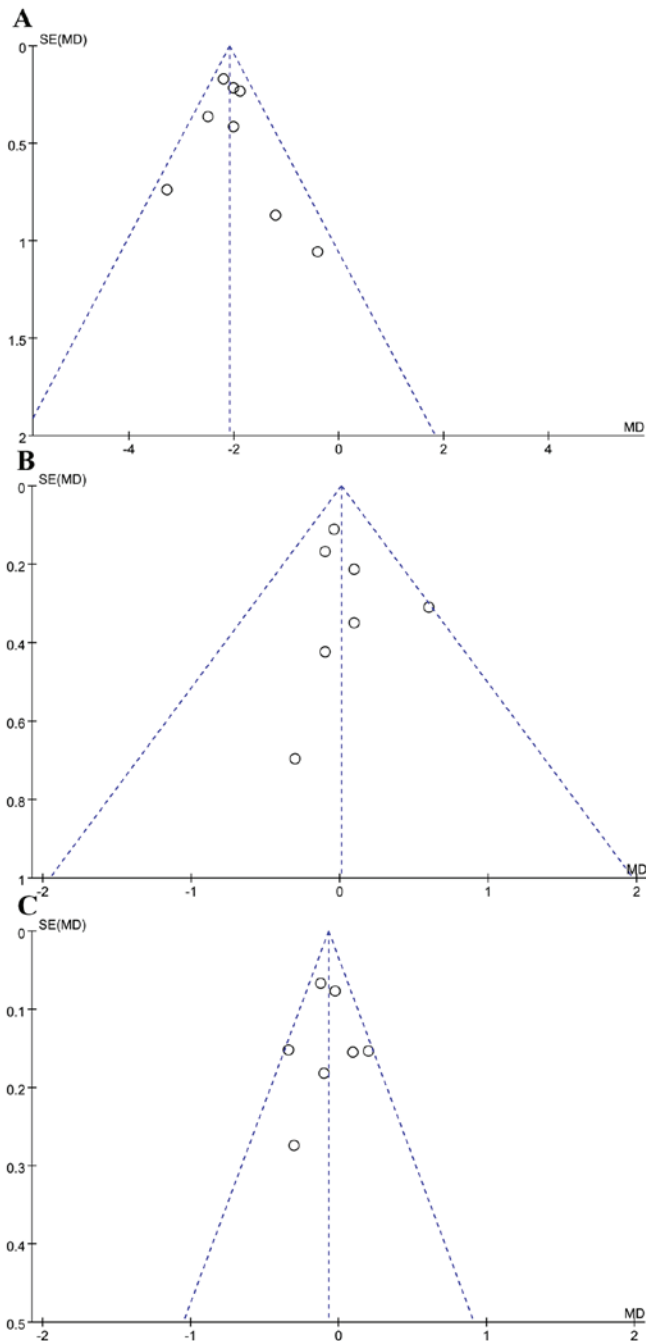


Figure 8. Funnel plots for assessment of bias of studies on the effects of liraglutide in patients with diabetic nephropathy. (A) Body mass index; (B) fasting blood glucose; (C) glycosylated hemoglobin A1c. MD, mean difference; SE, standardized effect.

released GLP-1 reaches the systemic circulation; most GLP-1 is degraded by the enzyme dipeptidyl peptidase-4 (25). Therefore, GLP-1 receptor agonists were developed and introduced in the clinic for improving the levels of internal GLP-1, increase insulin secretion and reduce blood glucose levels. Furthermore, previous studies have indicated that the GLP-1 receptor is produced not only in the pancreas, but also in the kidneys (25,26). The aim of the present meta-analysis was to determine whether liraglutide exhibits a renoprotective effect.

The meta-analysis included 1,187 patients; most of the trials included had a randomized double-blinded parallel control

design. UACR, UAER and Scr were selected as ideal markers for assessment of kidney function, as they are relatively inert by age, sex, BMI and inflammatory conditions (27,28). In addition, according to the 5 distinct stages of chronic kidney diseases, the 13 studies on early DN included were divided into stages I-II and stage III. Regardless of the DN stage, the present results suggested that liraglutide may have positive effects on lowering UACR, UAER and Scr. It also offered the benefit of producing anti-inflammatory responses in patients with stage-III DN.

Importantly, the NF- κ B signaling pathway is the major pathway that regulates the effect of inflammatory cytokines, including TNF- α . A previous study suggested that liraglutide downregulated the levels of NF- κ B by binding to GLP-1 receptor to inhibit the levels of TNF- α , IL-6 and monocyte chemoattractant protein-1 in the kidneys of a patient with diabetes (29). The results of a previous study suggested that liraglutide had anti-fibrotic and anti-inflammatory effects in the kidney (29).

With regard to blood glucose and lipid levels, the present meta-analysis indicated that liraglutide reduced the BMI, blood lipids and PBG levels. However, liraglutide only appeared to have an effect on PBG but provided no apparent benefit on FBG and HbA1c, probably due to most control groups receiving insulin. Compared with insulin, liraglutide had little effect on FBG and HbA1c, which is in agreement with a previous clinical study (30). Furthermore, although the Egger's test and funnel plots indicated no publication bias in BMI, FBG and HbA1c, it is likely that other biases existed in the studies examined. For example, allocation concealment, blinding of participants and personnel and outcome assessment, and incomplete outcome data were not clear in these included trials, which may be the main reasons of potential biases. Regarding adverse events, only 5 studies in all included trials reported adverse events. Up until now, the number of trials referring on the adverse events is too limited to make any conclusion for the safety of liraglutide. Hence, future clinical trials should perform rigorous investigations regarding the safety of liraglutide.

In conclusion, the present meta-analysis indicated that compared with the control treatment, liraglutide reduced proteinuria, improved renal function and produced an anti-inflammatory effect in patients with incipient DN. These results may serve as a basis to guide the clinical application of liraglutide.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

WL and JY were involved in the conceptualization of the study. TT and WS performed the electronic database searches. JY and JM performed analysis of the data. JY and TT assessed the quality of evidence and participated in outlining the inclusion and exclusion criteria. WL and JM provided final approval of all procedures. WL wrote and reviewed the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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