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Is polyethylene glycol loxenatide 100 μg the preferred glucagon-like peptide-1 receptor agonist for type 2 diabetes mellitus? A meta-analysis and trial sequential analysis

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Abstract. – OBJECTIVE: This study aimed to systematically evaluate the efficacy, safety and optimal dose of polyethylene glycol loxenatide (PEX168) for treating type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS: Clinical trials of PEX168 for T2DM were identified in 8 databases, with a build time limit of January 2023. Included studies were subjected to meta-analysis and trial sequential analysis (TSA).

RESULTS: On the efficacy endpoint, the meta-analysis showed that PEX168 100 μg significantly reduced 0.86% glycated hemoglobin type A1c (HbA1c) (MD -0.86, 95% CI -1.02 – -0.70, $p<0.00001$), 1.11 mmol/L fasting plasma glucose (FPG) (MD -1.11, 95% CI -1.49 – -0.74, $p<0.00001$) and 1.91 mmol/L 2h postprandial glucose (PPG) (MD -1.91, 95% CI -3.35 – -0.46, $p=0.01$) compared with placebo. The TSA showed that all these benefits were conclusive. On safety endpoints, total adverse events (AEs), gastrointestinal (GI) AEs, serious AEs, and hypoglycemia were comparable to placebo for PEX168 100 μg ($p>0.05$). In the dose comparison, the HbA1c, FPG, and 2h PPG of PEX168 200 μg were comparable to 100 μg ($p>0.05$), while GI AEs were significantly higher than 100 μg (RR=2.84, 95% CI 1.64-4.93, $p=0.0002$).

CONCLUSIONS: PEX168 100 μg can significantly lower blood glucose and does not increase the risk of total AEs, GI AEs, and hypoglycemia, which may be a preferred glucagon-like peptide-1 receptor agonist for type 2 diabetes mellitus.

Key Words:
Polyethylene glycol loxenatide, Type 2 diabetes mellitus, Meta-analysis, Trial sequential analysis, Harbord.

Introduction

Diabetes remains a major threat to human health worldwide[1]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for approximately 90% of people with diabetes[1]. Relative insulin deficiency due to insulin resistance is the main cause of the development of T2DM[2], and abnormally high fasting plasma glucose (FPG) and postprandial glucose (PPG) are the main manifestations of T2DM. The long-term hyperglycemic state will cause peripheral vascular disease and neuropathy and induce many complications such as diabetic cardiomyopathy, diabetic nephropathy, diabetic retinopathy[2], and even multi-organ failure, which is the main cause of death[3]. According to previous scholars[4], approximately 4.2 million adults worldwide died of diabetes in 2019, and health expenditures for diabetes and its complications amount to $760 billion, placing a huge burden on the global healthcare system. As T2DM progresses, most patients eventually require insulin for glycemic control, and subcutaneous insulin injections remain the mainstay of treatment for T2DM[5]. However, frequent dosing and pain during injection are major factors limiting the clinical use of insulin, as they reduce long-term patient compliance and consequently lead to suboptimal glycemic control[6]. Glucagon-like peptide-1 receptor agonist (GLP-1 RA), a new class of glucose-lowering agents with excellent glucose-lowering and weight-reducing effects, has been reported[7]. GLP-1 RA, represented by dulaglutide and semaglutide, reduces dos-

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ing frequency to once a week, thus significantly improving patient compliance[8]. Therefore, the American Association of Clinical Endocrinologists guidelines recommend GLP-1 RA as the drug of choice after metformin[9]. Although GLP-1 RA has improved the prognosis of patients with T2DM to some extent, its potential gastrointestinal (GI) risk remains a major challenge for clinicians[10] and has led to premature discontinuation of therapy in some patients[11,12]. Therefore, there is an urgent need for a long-acting GLP-1 RA with lower GI risk to achieve a safe, effective, and durable glucose-lowering strategy.

Polyethylene glycol loxenatide (PEX168) is the first China-developed GLP-1 RA with the frequency of once a week[13], which is produced by altering the chemical structure of exenatide at positions 2, 14, 28 and 39 of N-terminus and modifying branched polyethylene glycol[14]. Its mechanism of action is similar to that of exenatide, which can stimulate insulin secretion in high glucose state by activating GLP-1 receptor and lower blood glucose in a glucose-dependent manner[15]. Also, due to the chemical modification of polyethylene glycol, PEX168 is less susceptible to degradation by dipeptidyl peptidase 4 (DPP4)[16] and thus has a longer half-life and lower frequency of dosing. Notably, not only does PEX168 have excellent glucose-lowering effects and drug compliance, but low doses of PEX168 do not significantly increase GI adverse events (AEs) and hypoglycemia[16]. This is the first GLP-1 RA that does not significantly increase GI risk, suggesting that PEX168 may be a safer glucose-lowering agent for long-term use. Currently, there is no meta-analysis related to PEX168 for T2DM, and the evidence-based basis for PEX168 for T2DM remains to be elucidated. Therefore, this study intends to evaluate the efficacy, safety and optimal dose of PEX168 for the treatment of T2DM using the meta-analysis and trial sequential analysis (TSA).

Materials and Methods

This study strictly followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[17] and was registered in PROSPERO (CRD42023390471).

Literature Search

The China National Knowledge Infrastructure (CNKI, https://www.cnki.net/), WanFang (https://www.wanfangdata.com.cn/), Chinese Biology Medicine (CBM, http://www.sinomed.ac.cn/index.jsp), VIP (http://qikan.cqvip.com/), Embase (https://www.embase.com/), the Cochrane Library (https://www.cochranelibrary.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/) were searched for clinical studies of PEX168 in the treatment of T2DM. There are no regional and language restrictions, and the time limit is January 2,023. The subject headings cover PEX168, type 2 diabetes mellitus. Based on the subject terms, we expanded the free terms with the help of CKNI, CBM and MeSH databases, and then combined the subject terms and free terms for searching.

Inclusion and Exclusion Criteria

Inclusion criteria

1) Type of data: Randomized controlled trial.

2) Participants who met the basic diagnosis of T2DM[18].

3) Intervention: Patients in the experimental group were treated with PEX168, and the control group with a placebo.

4) Indicators: Glycosylated hemoglobin type A1c (HbA1c) was used as the primary efficacy endpoint. FPG, 2h PPG, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were used as secondary efficacy endpoints, total AEs, serious AEs, GI AEs, nausea, vomiting, diarrhoea and hypoglycemia were used as safety endpoints.

Exclusion criteria

1) Studies that did not use intervention blinding of participants.

2) Studies with unavailable data.

3) Studies with incomplete data.

4) Studies with repeated publications.

Literature Screening, Data Statistics and Risk of Bias

Above all, after importing all literature into Endnote X9 (The Thomson Scientific, Stanford, Connecticut, USA), the final studies were determined according to the inclusion and exclusion criteria. Then, we classified the included documents, extracted the basic features, and entered the data into the statistics table. After that, the risk of bias in these clinical trials was evaluated according to Cochrane guidelines (MRC Biostatistics Unit, Institute of Public Health, Cambridge CB2 0SR, UK).

All searches and screening were done independently by Xinyu Yang and Keke Tong, with deviations and disagreements decided by Pei Liu.

Statistical Analysis

We used Revman 5.3 (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) and TSA0.9.5.10 Beta software (The Copenhagen Trial Unit, Copenhagen, Denmark) to conduct the meta-analysis and TSA. When the indicators were continuous variables, mean difference (MD) was used as the effect size. When the indicator was a dichotomous variable, risk ratio (RR) was used as the effect size. Heterogeneity was analyzed by I^2-test and Q-test. If $I^2 \geq 50\%$ and $p \leq 0.1$, significant heterogeneity was observed, and random effects model analysis was used[19]. Otherwise, fixed-effect model analysis was used. The statistical significance was set to $p=0.05$. In the TSA, the original results were conclusive if the cumulative Z-value crossed the required information size or TSA bound[19]. Harbord-weighted linear regression was used to test for publication bias, and no significant publication bias existed if $p>0.1$[20]. The quality evaluation of evidence was based on the GRADE guidelines (McMaster University, Hamilton, ON, Canada), and the quality of evidence for each indicator was assessed comprehensively.

Results

Literature Screening

A total of 99 studies were retrieved, and 48 studies were screened out due to duplication or other reasons. After reading the title and abstract, 37 studies were screened out. After reading the full-text, 11 studies were removed, and 3 studies were finally included[21-23]. The flow chart of the literature screening is shown in Figure 1.

Basic Characteristics of the Included Studies

A total of 3 clinical studies with a total sample size of 1,012 cases were included, including 344 cases using PEX168 100 μg, 330 cases using PEX168 200 μg, and 338 cases using placebo. The study centers of the included studies were located in China and all studies used HbA1c as the primary efficacy endpoint and FPG and 2h PPG as secondary efficacy endpoints. The basic characteristics of the included studies are shown in Table I.

Risk of Bias Assessment

All three included studies were at low risk of bias in all domains. The risk of bias in the included studies is shown in Figure 2.

Blood Glucose-Related Efficacy Endpoints

PEX168 100 μg vs. placebo

The meta-analysis showed that PEX168 100 μg significantly reduced HbA1c by 0.86% (MD -0.86, 95% CI -1.02 to -0.70, $p<0.00001$), FPG by 1.11 mmol/L (MD -1.11, 95% CI -1.49 to -0.74, $p<0.00001$) and 2h PPG by 1.91 mmol/L (MD -1.91, 95% CI -3.35 to -0.46, $p=0.01$) when compared with placebo. Sensitivity analysis indicated that the heterogeneity of 2h PPG was derived from the study of Chen et al[21], and there was no significant change in the combined results after removing that study (MD -1.12, 95% CI -1.75 to -0.50, $p=0.0004$), suggesting that the results were robust. The TSA demonstrated conclusive benefit for HbA1c, FPG and 2h PPG. The evaluation of evidence quality displayed high-quality evidence for HbA1c and FPG and medium-quality evidence for 2h PPG, as shown in Figure 3.

PEX168 200 μg vs. placebo

The meta-analysis showed that PEX168 200 μg significantly reduced HbA1c by 1.09% (MD -1.09, 95% CI -1.46 to -0.73, $p<0.00001$), FPG by 1.42 mmol/L (MD -1.42, 95% CI -2.05 to -0.80, $p<0.00001$) and 2h PPG by 2.22 mmol/L (MD -2.22, 95% CI -3.35 to -1.10, $p=0.0001$) when compared with placebo. Sensitivity analysis displayed that the heterogeneity of these indicators was derived from the study of Gao et al[22], and the combined HbA1c (MD -1.24, 95% CI -1.48 to -1.00, $p<0.00001$), FPG (MD -1.74, 95% CI -2.28 to -1.21, $p<0.00001$) and 2h PPG (MD -2.71, 95% CI -3.35 to -1.88, $p<0.00001$) obtained after removing this study did not change significantly, suggesting that these results were robust. The TSA indicated conclusive benefits for HbA1c, FPG and 2h PPG. The evaluation of evidence quality showed moderate quality of evidence for HbA1c, FPG, and 2h PPG, as shown in Figure 4.

PEX168 200 μg vs. PEX168 100 μg

The meta-analysis indicated that HbA1c ($p=0.15$), FPG ($p=0.23$) and 2h PPG ($p=0.40$) of PEX168 200 μg were comparable to those of PEX168 100 μg. Sensitivity analysis demonstrated that the heterogeneity of HbA1c was derived

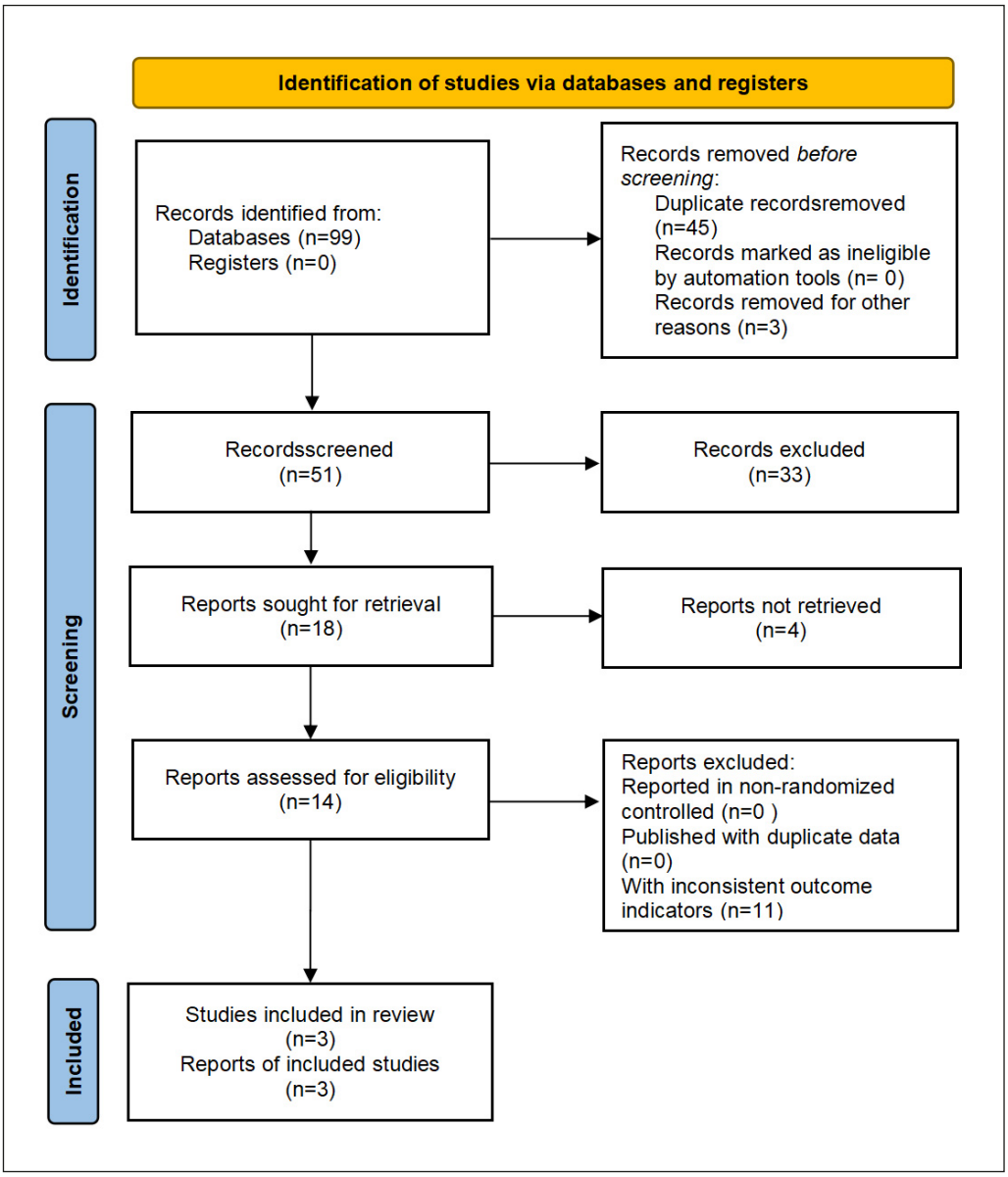

Figure 1. Flow chart of literature screening.

from the study of Gao et al[22], and after removing this study, the combined results showed a significant decrease in HbA1c (MD -0.32, 95% CI -0.54 – -0.10, p=0.004), suggesting a high sensitivity of the combined results. 2h PPG heterogeneity was derived by Shuai et al[23], and after removing this study, the combined results did not change significantly (MD -0.43, 95% CI -1.43-0.57, p=0.40), suggesting a high confidence of the combined results. The TSA showed that none of these results observed at the current information level were conclusive. The evaluation of evidence quality displayed a medium quality of evidence for FPG and a low quality of evidence for HbA1c and 2h PPG, as shown in Figure 5.

Other Efficacy Endpoints

The meta-analysis displayed that the levels of TC (p=0.64), TG (p=0.53), LDL-C (p=0.57), HDL-C (p=0.86), SBP (p=0.26) and DBP (p=0.53) in the PEX168 100 μg were not significantly different from those in the placebo group. The levels of TC (p=0.27), TG (p=0.41), LDL-C (p=0.27), HDL-C (p=0.51), SBP (p=0.80) and DBP (p=0.85) in the PEX168 200 μg were also not significantly different from those in the place-

Table I. Table of basic characteristics of included studies.

Author Name	Center	Patient Number	Treatment Duration (weeks)	Intervention	Number Randomized	Age (Years)	Male N/(%)	Disease Duration (years)	HbA1c (%)	Body weight (kg)	BMI (kg/m²)
Chen et al[21], 2017	China	118	12	PEX168 100 μg QW	41	52.6	22 (53.66)	4.4	8.23	/	27.2
				PEX168 200 μg QW	39	49.8	22 (56.41)	4.0	8.34	/	26.3
				Placebo	38	53.5	26 (68.42)	6.5	8.28	/	27.2
Gao et al[22], 2020	China	533	24	PEX168 100 μg QW	179	53.6	102 (57)	4.3	8.50	71.2	26.0
				PEX168 200 μg QW	175	52.8	106 (60.6)	4.8	8.50	73.6	26.6
				Placebo	179	52.3	98 (54.7)	4.7	8.60	73.8	26.9
Shuai et al[23], 2021	China	361	24	PEX168 100 μg QW	124	50.5	83 (66.9)	1.0	8.50	74.3	27.0
				PEX168 200 μg QW	116	52.4	64 (55.2)	1.5	8.50	71.9	26.4
				Placebo	121	51.5	88 (72.7)	1.7	8.60	72.8	26.3

PEX168, polyethylene glycol loxenatide.

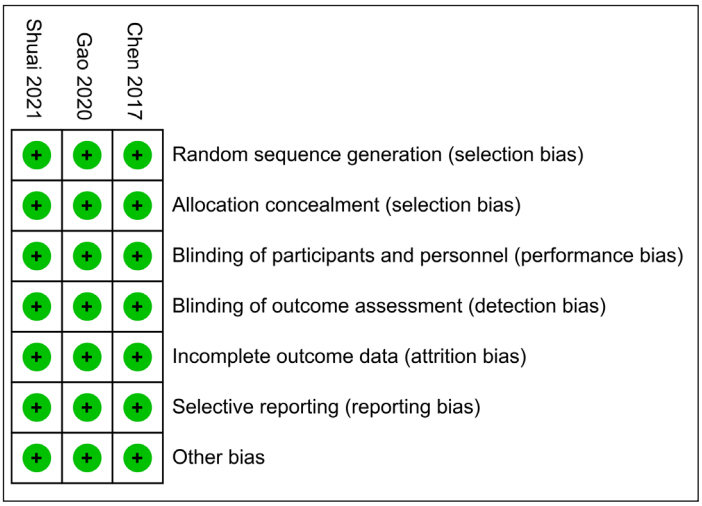

Figure 2. Risk of bias graph.

bo group. The levels of TC (p=0.80), TG (p=0.97), LDL-C (p=0.18), HDL-C (p=0.51), SBP (p=0.38) and DBP (p=0.34) were no significant differences between the PEX168 200 μg and PEX168 100 μg groups. The TSA indicated that none of these results observed for the current information size were conclusive. The evaluation of evidence quality showed low or moderate quality of evidence for these indicators, as shown in Table II.

Safety Endpoints

PEX168 100 μg vs. placebo

The meta-analysis demonstrated that PEX168 100 μg significantly increased nausea compared with placebo (RR 4.06, 95% CI 1.03-15.96, p=0.04), while total AEs (p=0.79), serious AEs (p=0.85), GI AEs (p=0.91), vomiting (p=0.14), diarrhea (p=0.90) and hypoglycemia (p=0.18)

Table II. Meta-analysis and TSA results of other efficacy endpoints of PEX168 for T2DM.

Outcome	I^2	MD (95% CI)	p	TSA	Quality of evidence
PEX168 100 μg *vs.* placebo					
TC (mmol/L)	91	-0.17 (-0.87, 0.54)	0.64	No	Low
TG (mmol/L)	0	0.14 (-0.29, 0.56)	0.53	No	Moderate
LDL-C (mmol/L)	62	-0.08 (-0.36, 0.20)	0.57	No	Low
HDL-C (mmol/L)	0	0.00 (-0.04, 0.05)	0.86	No	Moderate
SBP (mmHg)	6	1.51 (-1.14, 4.15)	0.26	No	Moderate
DBP (mmHg)	62	1.04 (-2.19, 4.28)	0.53	No	Low
PEX168 200 μg *vs.* placebo					
TC (mmol/L)	66	-0.18 (-0.50, 0.14)	0.27	No	Low
TG (mmol/L)	0	0.17 (-0.23, 0.56)	0.41	No	Moderate
LDL-C (mmol/L)	97	-0.54 (-1.50, 0.42)	0.27	No	Low
HDL-C (mmol/L)	0	-0.02 (-0.06, 0.03)	0.51	No	Moderate
SBP (mmHg)	30	0.34 (-2.29, 2.97)	0.80	No	Moderate
DBP (mmHg)	72	0.38 (-3.43, 4.18)	0.85	No	Low
PEX168 200 μg *vs.* PEX168 100 μg					
TC (mmol/L)	65	-0.05 (-0.42, 0.33)	0.80	No	Low
TG (mmol/L)	69	0.01 (-0.52, 0.54)	0.97	No	Low
LDL-C (mmol/L)	0	-0.11 (-0.27, 0.05)	0.18	No	Moderate
HDL-C (mmol/L)	0	-0.02 (-0.07, 0.03)	0.51	No	Moderate
SBP (mmHg)	0	-1.17 (-3.75, 1.42)	0.38	No	Moderate
DBP (mmHg)	0	-0.91 (-2.80, 0.97)	0.34	No	Moderate

MD, mean difference; CI, confidence interval; TSA, trial sequential analysis; PEX168, polyethylene glycol loxenatide; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table III. Meta-analysis and TSA results of safety endpoint of PEX168 for T2DM.

Outcome	PEX168 arm (events/total)	Placebo arm (events/total)	I^2	RR (95% CI)	*p*	TSA	Quality of evidence
PEX168 100 μg *vs.* placebo							
Total AEs	163/344	157/338	0	1.02 (0.87, 1.20)	0.79	No	Moderate
Serious AEs	9/303	7/300	51	1.16 (0.25, 5.34)	0.85	No	Low
GI AEs	15/165	14/159	0	1.04 (0.52, 2.08)	0.91	No	Moderate
Nausea	10/344	2/338	9	4.06 (1.03, 15.96)	0.04	No	Moderate
Vomiting	4/344	0/338	0	4.93 (0.58, 42.01)	0.14	No	Moderate
Diarrhea	9/344	7/338	50	1.12 (0.20, 6.23)	0.90	No	Low
Hypoglycemia	6/303	2/300	0	2.97 (0.61, 14.58)	0.18	No	Moderate
PEX168 200 μg *vs.* placebo							
Total AEs	168/330	157/338	35	1.10 (0.94, 1.28)	0.23	No	Moderate
Serious AEs	8/291	7/300	0	1.18 (0.43, 3.22)	0.75	No	Moderate
GI AEs	40/155	14/159	45	2.95 (1.67, 5.21)	0.0002	Yes	High
Nausea	29/330	2/338	0	11.93 (3.33, 42.65)	0.0001	Yes	High
Vomiting	20/330	0/338	0	14.57 (2.82, 75.33)	0.001	Yes	High
Diarrhea	17/330	7/338	20	2.49 (1.04, 5.93)	0.04	No	Moderate
Hypoglycemia	3/303	2/300	0	1.48 (0.25, 8.80)	0.67	No	Moderate
PEX168 200 μg *vs.* PEX168 100 μg							
Total AEs	168/330	163/344	0	1.08 (0.92, 1.25)	0.35	No	Moderate
Serious AEs	8/291	9/303	0	0.92 (0.36, 2.35)	0.86	No	Moderate
GI AEs	40/155	15/165	0	2.84 (1.64, 4.93)	0.0002	Yes	High
Nausea	29/330	10/344	18	3.06 (1.53, 6.15)	0.002	Yes	High
Vomiting	20/330	4/344	0	4.80 (1.75, 13.15)	0.002	Yes	High
Diarrhea	17/330	9/344	0	1.92 (0.88, 4.17)	0.10	No	Moderate
Hypoglycemia	3/303	6/303	0	0.50 (0.13, 1.98)	0.32	No	Moderate

PEX168, polyethylene glycol loxenatide; RR, risk ratio; CI, confidence interval; TSA, trial sequential analysis; AEs, adverse events; GI, gastrointestinal.

were all comparable to placebo. Sensitivity analysis showed that the heterogeneity of vomiting was derived from the study of Gao et al[22], and there was no significant change in the combined results after removing that study (RR 0.52, 95% CI 0.14-1.87, p=0.32), suggesting that the results were robust. The TSA indicated that these results observed in the current informative volume need to be justified by more studies. The evaluation of evidence quality suggested the moderate quality of evidence for total AEs, GI AEs, nausea, vomiting, and hypoglycemia, and low quality of evidence for serious AEs and diarrhea, as shown in Table III.

PEX168 200 μg vs. placebo

The meta-analysis demonstrated that PEX168 200 μg significantly increased GI AEs (RR 2.95, 95% CI 1.67 to 5.21, p=0.0002), nausea (RR 11.93, 95% CI 3.33 to 42.65, p=0.0001), vomiting (RR 14.57, 95% CI 2.82 to 75.33, p=0.001) and diarrhea (RR 2.49, 95% CI 1.04 to 5.93, p=0.04) compared with placebo, whereas total AEs (p=0.23), serious AEs (p=0.75) and hypoglycemia (p=0.67) were all comparable to placebo. The TSA showed conclusive results for GI AEs, nausea, and vomiting. The evaluation of evidence quality displayed high-quality evidence for GI AEs, nausea and vomiting, and moderate-quality evidence for total AEs, serious AEs, diarrhea, and hypoglycemia, as shown in Table III.

PEX168 200 μg vs. PEX168 100 μg

The meta-analysis demonstrated that PEX168 200 μg significantly increased GI AEs (RR 2.84, 95% CI 1.64-4.93, p=0.0002), nausea (RR 3.06, 95% CI 1.53-6.15, p=0.002) and vomiting (RR 4.80, 95% CI 1.75-13.15, p=0.002) compared to PEX168 100 μg, while total AEs (p=0.35), serious AEs (p=0.86), diarrhea (p=0.10) and hypoglycemia (p=0.32) were comparable. The TSA showed conclusive results for GI AEs, nausea, and vomiting. The evaluation of evidence quality indicated high quality of evidence for GI AEs, nausea, and vomiting, and moderate quality of evidence for other indicators (Table III). A summary of the results of the two-by-two comparison between PEX168 200 μg, PEX168 100 μg and placebo is shown in Figure 6.

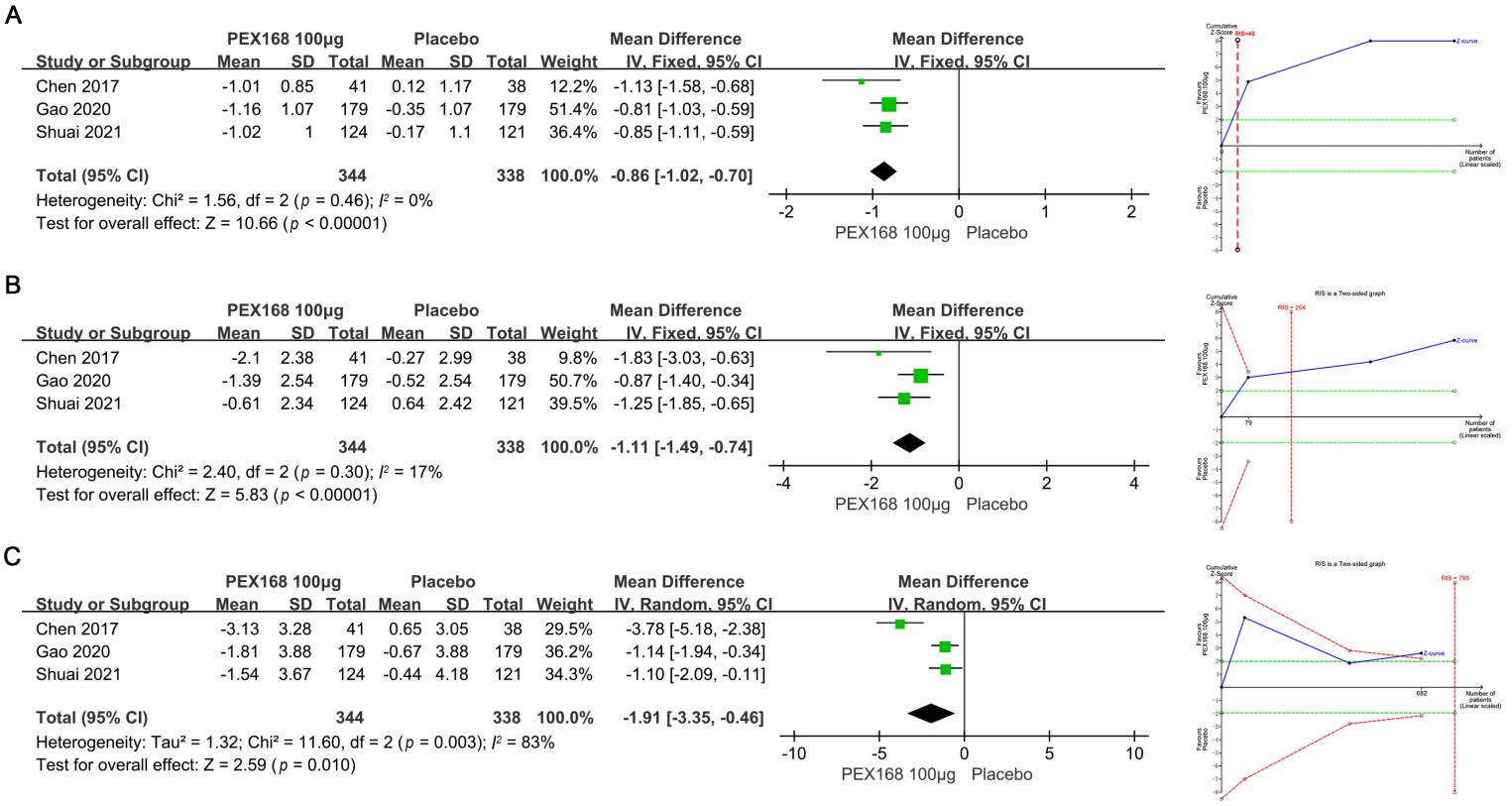

Figure 3. Meta-analysis and TSA results of blood glucose in PEX168 100 μg *vs.* Placebo for T2DM. **A**, HbA1c; (**B**) FPG; (**C**) 2h PPG. TSA, trial sequential analysis; PEX168, polyethylene glycol loxenatide; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin type A1c; FPG, fasting plasma glucose; 2h PPG, 2h postprandial glucose.

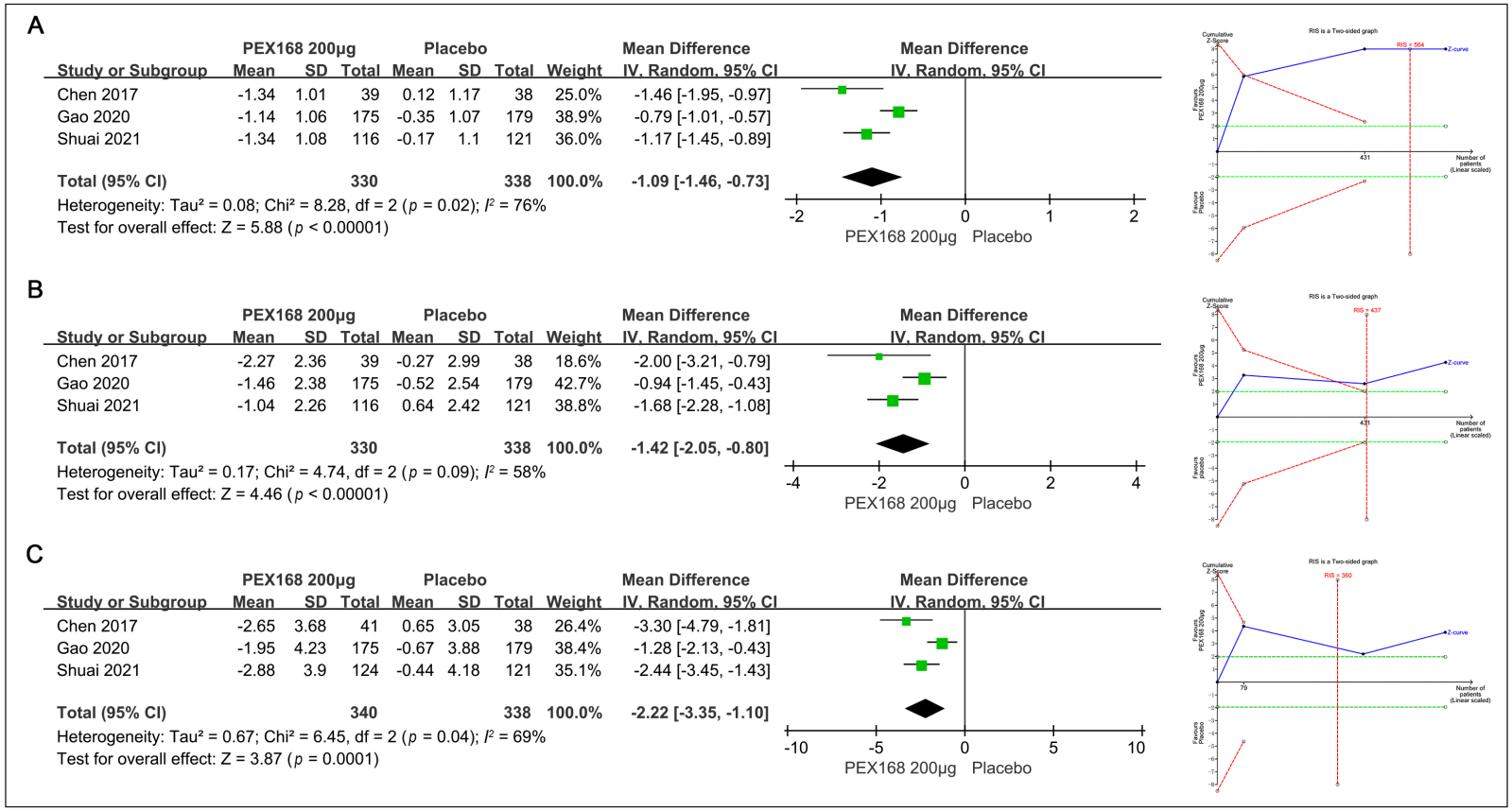

Figure 4. Meta-analysis and TSA results of blood glucose in PEX168 200 μg *vs.* Placebo for T2DM. **A**, HbA1c; (**B**) FPG; (**C**) 2h PPG. TSA, trial sequential analysis; PEX168, polyethylene glycol loxenatide; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin type A1c; FPG, fasting plasma glucose; 2h PPG, 2h postprandial glucose.

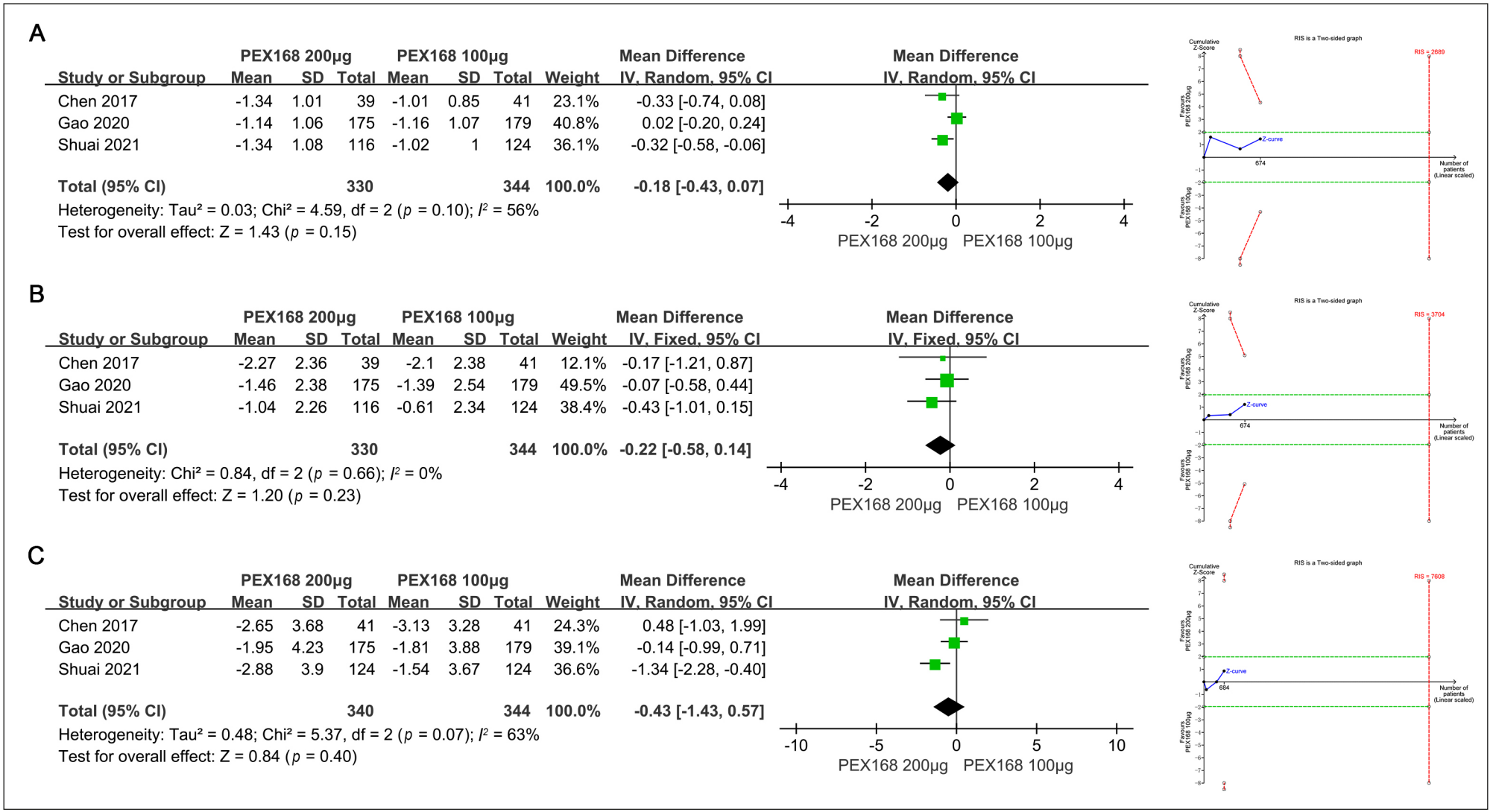

Figure 5. Meta-analysis and TSA results of blood glucose in PEX168 200 µg *vs.* PEX168 100 µg for T2DM. **A**, HbA1c; (**B**) FPG; (**C**) 2h PPG. TSA, trial sequential analysis; PEX168, polyethylene glycol loxenatide; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin type A1c; FPG, fasting plasma glucose; 2h PPG, 2h postprandial glucose.

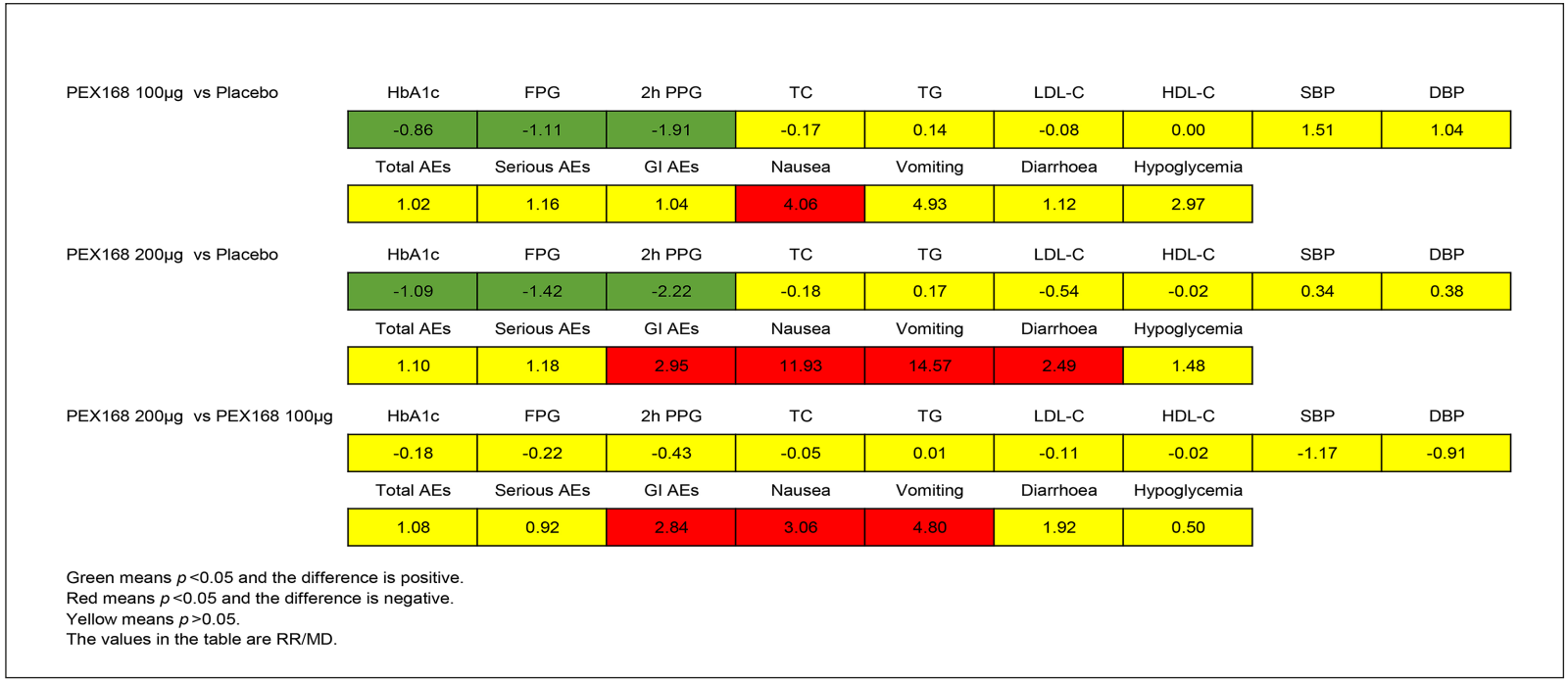

Figure 6. Summary chart of meta-analysis results.

Publication Bias

The funnel plot of total AEs showed a more symmetrical scatter distribution on both sides, and Harbord regression showed p=0.347, suggesting that there was no significant publication bias, as shown in Figure 7.

Discussion

GLP-1 RA is one of the most well-developed glucose-lowering agents, which can lower blood glucose by stimulating insulin release and inhibiting glucagon secretion in a glucose-dependent manner[21,24,25], and it also reduces body weight by delaying gastric emptying and reducing appetite[26]. Therefore, GLP-1 RA was recommended by guidelines as the drug of choice after metformin[9]. Exenatide is the first GLP-1 RA to be used in the treatment of T2DM and has shown good results in lowering blood glucose and reducing body weight in clinical trials[27]. Unfortunately, exenatide requires twice-daily subcutaneous injections[28,29], which may lead to poor patient compliance in long-term treatment and compromise the clinical efficacy of the drug. As research progressed, liraglutide reduced the dosing frequency to once daily, and GLP-1 RAs represented by dulaglutide and semaglutide even reduced the dosing frequency to once a week[30], greatly improving the drug compliance problem. However, the GI risk of GLP-1 RAs, such as dulaglutide and semaglutide, remain prominent, and GI AEs are a major cause of premature treatment termination in patients with T2DM[31]. Therefore, it is imperative to develop a durable and effective GLP-1 RA with lower GI risk. PEX168, a novel long-acting GLP-1 RA obtained by amino acid modification and polyethylene glycolization of exenatide, may have a promising clinical application with good glucose-lowering effect, drug compliance, and lower GI risk[32]. This meta-analysis and TSA included three clinical trials with 1,012 samples and is the first publication to study PEX168 to assess the efficacy, safety, and preferred dose of PEX168 for treating patients with T2DM.

In terms of glycemic endpoints, this meta-analysis demonstrated that compared to placebo, PEX168 100 μg significantly reduced HbA1c by 0.86%, FSG by 1.13 mmol/L, and 2h PPG by 1.91 mmol/L, and PEX168 200 μg significantly reduced HbA1c by 1.09%, FSG by 1.42 mmol/L and 2h PPG by 2.22 mmol/L. The TSA indicated that these benefits were conclusive, suggesting that PEX168 had a significant glucose-lowering effect. The glucose-lowering mechanism of PEX168 is similar to other long-acting GLP-1RAs in two ways.

First, it lowers blood glucose by promoting glucose-dependent insulin secretion and reducing glucagon secretion[33]. Second, it also regulates blood glucose stability by inhibiting gastric emptying and delaying food absorption[34]. Also, the polyethylene glycol in the structure of PEX168 can delay the degradation of the peptide chain by DPP4[35,36], thereby prolonging its half-life, reducing the frequency of dosing, and improving patient compliance[37]. The glucose-lowering effect of PEX168 was reported to be significantly better than that of conventional GLP-1 RA exenatide, and its HbA1c-lowering effect lasted until week 52[22,23]. This implies that PEX168 may have a long-term glycemic control effect. In addition, Chen et al[21] reported that PEX168 could dose-dependently

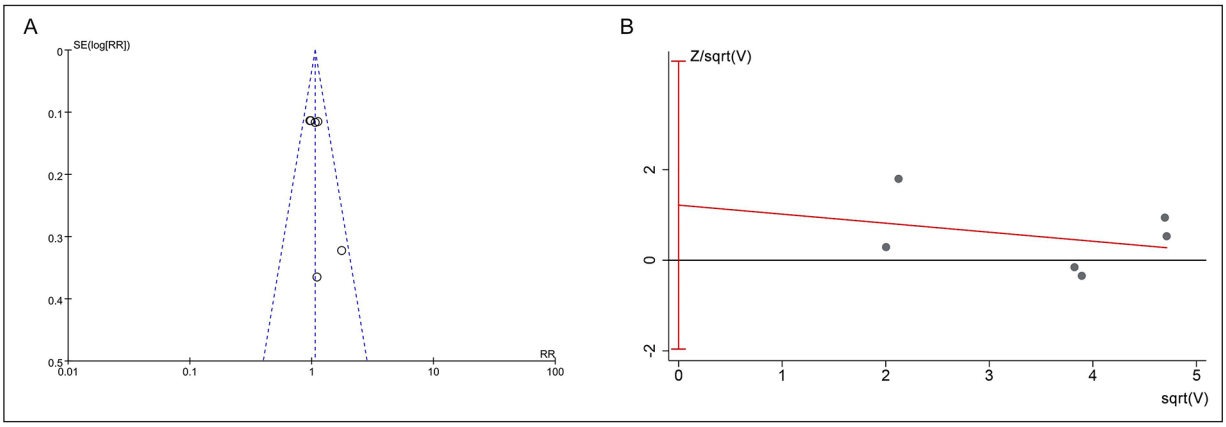

Figure 7. Publication bias assessment. **A**, Funnel plot; (**B**) Harbord regression.

elevate HOMA-β, suggesting that PEX168 could modulate pancreatic β-cell function and thus reduce insulin resistance. These results suggest that PEX168 may have a higher clinical value.

On lipid-related endpoints, this meta-analysis confirmed that TC, TG, LDL-C and HDL-C were comparable to placebo for PEX168 100 μg and PEX168 200 μg, suggesting that PEX168 did not have a significant effect on lipid levels in patients with T2DM. The TSA demonstrated that the results observed with the current information size were not definitive and required validation through additional relevant studies. Interestingly, the results of Chen et al[19] displayed that PEX168 100 μg was able to reduce TC by 0.44 mmol/L and LDL-C by 0.18 mmol/L, and PEX168 200 μg was able to reduce TC by 0.26 mmol/L and LDL-C by 0.33 mmol/L. This decreasing trend was statistically different, which indicated that PEX168 may have the potential to reduce TC and LDL-C. Zhang et al[16] showed significant lipid-lowering effects of high doses of PEX168 and found that 0.3 mg/kg, 0.4 mg/kg, and 1 mg/kg of PEX168 significantly reduced TC and increased HDL-C in mice with T2DM. Although there is increasing evidence that PEX168 has the potential to reduce blood lipids, we did not find this benefit in the meta-analysis and TSA. The role of PEX168 in modulating lipids remains controversial and needs to be further explored in subsequent studies. On blood pressure-related endpoints, SBP and DBP were not significantly different from placebo for PEX168 100 μg and PEX168 200 μg, implying that PEX168 does not have a risk of elevated blood pressure, and the TSA suggested that this result needed to be validated in more relevant studies. In summary, we can determine that PEX168 does not have a risk of increasing lipids and blood pressure and may have a potential benefit in regulating lipids.

In terms of safety endpoints, this study showed that the total AEs, serious AEs and hypoglycemia for PEX168 100 μg and 200 μg were comparable to placebo, implying a good overall safety profile for PEX168. This meta-analysis indicated that PEX168 100 μg had significantly higher nausea than placebo, while GI AEs, vomiting and diarrhea were all comparable to placebo. In addition, Chen et al[21] noted that nausea may gradually decrease over time of dosing, suggesting that the long-term safety of PEX168 100 μg may be better. Of interest, PEX168 100 μg only increased the incidence of nausea (2.91%), but not other single GI AEs or total GI AEs, implying that PEX168 100 μg has a good GI safety profile. In previous studies[10], GI AEs were the main cause of AEs and discontinuation of GLP-1 RA. Therefore, the reliable GI safety makes PEX168 stand out among similar drugs. This study also showed that PEX168 200 μg had significantly higher GI AEs, nausea, vomiting and diarrhea than placebo, and the TSA displayed conclusive results for GI AEs, nausea and vomiting, suggesting definitive evidence that PEX168 200 μg increases GI AEs. Although PEX168 200 μg increased GI risk, the included studies indicated that the incidence of all GI AEs was <10% and most of them were mild, suggesting that PEX168 200 μg also has a good safety profile.

In the dose comparison, this meta-analysis showed that the HbA1c, FPG and 2h PPG of PEX168 200 μg were comparable to those of PEX168 100 μg, suggesting that there was no significant difference in the glucose-lowering effect between the two groups. The sensitivity analysis revealed that Gao et al[22] contributed to the heterogeneity in HbA1c, yet we did not identify any clinical or methodological heterogeneity in this study. Therefore, it may be attributed to statistical heterogeneity. Notably, the combined results after the removal of Gao et al[22] displayed that PEX168 200 μg significantly reduced HbA1c by 0.32% compared to 100 μg (MD -0.32, 95% CI -0.54 to -0.10, p=0.004), implying that PEX168 200 μg may have a stronger effect in reducing HbA1c. Unfortunately, there is currently insufficient evidence to confirm that the glucose-lowering effect of PEX168 200 μg is significantly better than that of 100 μg, and we look forward to future studies to explore the optimal dose for PEX168. This meta-analysis also showed that the TC, TG, LDL-C, HDL-C, SBP and DBP of PEX168 200 μg were all comparable to those of PEX168 100 μg, suggesting that the effects of both groups on lipids and blood pressure were similar. In terms of safety endpoints, the total AEs, serious AEs, diarrhea, and hypoglycemia of PEX168 200 μg were comparable to those of PEX168 100 μg, suggesting that the overall safety of the two groups was comparable. In contrast, the GI AEs, nausea and vomiting of PEX168 200 μg were significantly higher than those of PEX168 100 μg, and the TSA confirmed that these three results were conclusive, implying that the GI risk of PEX168 200 μg was significantly higher than that of PEX168 100 μg. It is thus clear that the glucose-lowering effect of PEX168 200 μg was comparable to that of 100 μg, but the risk of GI risk is significantly higher

than that of 100 μg. Therefore, we recommend 100 μg as the preferred clinical dose of PEX168 to achieve equivalent glucose reduction while minimizing the risk of AEs.

Although this study has undergone a series of reasonable analyses, there are certain limitations. First, the total sample size was not large enough and the number of study subjects belonging to various regions, age groups, and weight classes was not broad enough. Second, Gao et al[22] and Chen et al[21] had a background of co-administration of metformin rather than PEX168 alone, which means that the results of this study cannot be used to explain the efficacy and safety of PEX168 alone. Third, there are no studies to confirm whether there is an interaction between PEX168 and metformin, so it is unclear whether metformin affects the efficacy of PEX168. Finally, a meta-analysis of body weight could not be performed because of the different statistical forms of data about body weight in the included literature, which implies that the effect of PEX168 on body weight in patients with T2DM still needs to be further explored. Notably, the studies by Gao et al[22] and Shuai et al[23] did not find a weight-reducing effect of PEX168, whereas Wang et al[38] and Tian et al[39] reported that PEX168 was able to significantly reduce patients' weight and body mass index (BMI). This difference in results may be related to the BMI baseline. Wang et al[38] included patients with a baseline BMI >30 kg/m^2, whereas Gao et al[22] and Shuai et al[23] included patients with a baseline BMI of 26.0-27.0 kg/m^2. In addition, Wu et al[8] noted that high doses of PEX168 had a definite effect on reducing body weight, and they found that 0.1 mg/kg of PEX-168 significantly reduced the body weight of simple obese mice. However, due to the lack of sufficient clinical evidence, the benefit of PEX168 in reducing body weight and BMI remains to be further explored in future studies.

For better research in the future, we sincerely hope that we can enhance the following points. First, different levels of research can be conducted. Studies with different populations in different regions can be conducted to expand the generalizability of the study. Second, the value of PEX168 in combination drug use should be studied in depth. Most patients with T2DM eventually need to control their blood glucose through combination drugs[5], so actively conducting clinical trials of PEX168 in combination with other glucose-lowering agents or insulin will help to more comprehensively assess the benefits and risks of PEX168 combination drugs and provide more evidence-based basis for its clinical application. Third, subsequent studies should extend the duration of drug treatment and follow-up. Patients with T2DM often need long-term medication, so long-term efficacy is the key to measuring the effectiveness of PEX168. Three of the included studies had a follow-up time of 24 weeks or less, and most of the efficacy data obtained were short-term results, lacking long-term efficacy results of PEX168. Future studies need to focus on the long-term effects of PEX168 in the treatment of T2DM and extend the duration of treatment and follow-up in clinical trials. We expect that clinical trials related to PEX168 will be further optimized and look forward to the benefits of PEX168 in patients with T2DM.

Conclusions

PEX168 100 μg can significantly reduce blood glucose in patients with T2DM without increasing total AEs, GI AEs, and hypoglycemia. Given the good clinical efficacy and safety profile of PEX 168 100 μg, it may be a preferential GLP-1 RA for treating T2DM.

Conflict of Interest

The authors declared that there are no conflicts of interest in this study.

Data Availability

The original data presented in this study are included in the manuscript. For more information, contact the corresponding author.

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Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Authors' Contributions

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