Role of Novel Glucagon-like Peptide-1 Receptor Analogue Polyethylene Glycol Loxenatide in Type 2 Diabetes: A Systematic Review and Meta-analysis

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Abstract

Background: Polyethylene glycol loxenatide (peg-loxenatide) is a novel glucagon-like peptide-1 receptor agonist developed and available for clinical use in China. This meta-analysis was performed as no meta-analysis has analysed the efficacy and safety of peg-loxenatide in type 2 diabetes (T2DM). **Methods:** Electronic databases were systematically reviewed for RCTs having patients living with T2DM receiving peg-loxenatide in treatment arm and placebo/any other diabetes medicine in control arm. The primary outcome was to evaluate changes in glycated haemoglobin. The secondary outcomes were to evaluate alterations in weight, blood pressure, fasting glucose, prandial glucose, lipids, and adverse events. **Results:** Data from four trials (718 patients) were analysed. Over 12–24 weeks of clinical use, HbA1c was significantly lower in patients receiving standard-dose peg-loxenatide (100 mcg/week) {MD -0.95% [95% confidence interval (CI): -1.19 to -0.71]; $P < 0.01$; $I^2 = 76\%$} and high-dose peg-loxenatide (200 mcg/week) [MD -1.15% (95% CI: -1.47 to -0.82); $P < 0.01$; $I^2 = 90\%$], as compared to placebo. Standard-dose peg-loxenatide was not associated with increased occurrence of nausea [RR 2.87 (95% CI: 0.56 to 14.72); $P = 0.21$; $I^2 = 10\%$], vomiting [RR 4.73 (95% CI: 0.53 to 41.88); $P = 0.16$; $I^2 = 0\%$], and anorexia [RR 0.78 (95% CI: 0.18 to 3.28); $P = 0.73$; $I^2 = 0\%$]. Occurrence of nausea [RR 16.85 (95% CI: 3.89 to 72.92); $P < 0.01$; $I^2 = 10\%$], vomiting [RR 15.90 (95% CI: 2.99 to 84.55); $P < 0.01$; $I^2 = 0\%$], and anorexia [RR 3.85 (95% CI: 1.24 to 11.88); $P = 0.02$; $I^2 = 0\%$] was significantly higher with high-dose peg-loxenatide, as compared to placebo. **Conclusion:** Peg-loxenatide (100 mcg/week) is the most appropriate dose for clinical use as it is associated with good glycaemic efficacy with minimal gastro-intestinal side effects.

Keywords: Glucagon-like peptide-1 analogue, loxenatide, meta-analysis, safety, type 2 diabetes

Introduction

Glucagon-like peptide-1 (GLP1) receptor analogues (GLP1RA) like exenatide, liraglutide, dulaglutide, semaglutide, and efpeglenatide have revolutionized antidiabetes pharmacotherapy in the past 2 decades with several agents available for clinical use globally.[1] Good glycaemic efficacy and durability, inducing satiety, weight loss, beneficial impacts on different components of metabolic syndrome (MetS), and improving cardiovascular outcomes, in diabetes patients with established cardiovascular disease or multiple risk factors for cardiovascular disease are some of the highlights of this class of medicine.[1] Enhancing glucose-dependent insulin secretion, slowing the gastric emptying, decreasing postprandial glucagon secretion, and decreasing food intake are some of the mechanisms of action of GLP1RAs.

Polyethylene glycol loxenatide (PEG-Lox), also known as peg-loxenatide, is a novel GLP1RA developed in China

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based on exenatide and is a 39-amino acid peptide, having a half-life much longer than that of exenatide, hence allowing once weekly administration.[2] Peg-loxenatide is formed by modifying the chemical structure of exendin-4 on the second, 14th, 28th, and 39th N-terminal positions, along with alteration of the branched polyethylene glycol.[2,3] The mean elimination half-life of PEG-Lox is 131.8–139.8 hours, having a mean t-max of 67.3 hours. Steady-state plasma PEG-Lox concentrations are attained only after 4 weeks of injections.[2]

Once weekly injection of peg-loxenatide has been approved and available for managing type 2 diabetes (T2DM) in China since January 2018 and has become quite popular in clinical practice.[4] Several randomized controlled trials (RCTs) have been published on use of peg-loxenatide in T2DM.[5,6] No meta-analysis till date has summarized the optimal dose and role of this novel GLP1RA in clinical practice. Hence, this meta-analysis analysed the role of peg-loxenatide for managing T2DM.

Methods

The meta-analysis was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines having PROSPERO registration number CRD42023404730.[7] Using PICOS criteria, RCTs involving people with T2DM receiving peg-loxenatide (100 mcg or 200 mcg per week) in the study group and placebo/any other medication in the control group were considered for this meta-analysis. Only trials having at least 12 weeks (3 months) of follow-up were included as it is the minimum follow-up needed to detect meaningful changes in the primary outcome HbA1c. Data from patients receiving peg-loxenatide 100 mcg/week and 200 mcg/week were analysed as they were the most commonly used doses in different studies for managing T2DM.[5,6] The primary outcome was to evaluate the changes in HbA1c. The secondary outcomes were alterations in blood pressure, body weight, fasting glucose (FPG), 2-hour post-prandial glucose (PPG), percentage of patients achieving HbA1c <6.5% and <7%, lipid parameters, and adverse events.

We systematically searched Embase database, Web of science, Cochrane library, Medline (PubMed), clinicaltrials.gov, CNKI database, ctri.nic.in, and Google scholar as either keywords or MESH terms: (peg-loxenatide) OR (loxenatide) OR (PEX168) AND (diabetes). Details have been elaborated in previous meta-analysis published by our group.[8]

Data extraction with regard to all the primary and secondary outcomes stated above was carried out independently by two authors. Multiple publications from the same group on the same cohort of patients were pooled together and considered as a single study for our meta-analysis. Details have been elaborated in previous meta-analysis published by our group.[8] The risk of bias assessment was performed by three authors using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 software. The different types of bias looked for have been elaborated in previous meta-analyses by our group.[8,9]

The international system of units (SI units) was used for all the analyses done. Continuous variable outcomes were presented as mean differences (MDs). For dichotomous variables, outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) and as hazard ratios (HRs) for adverse events. RevMan 5.4 was used for doing all the statistical analyses and generation of Forest plots in this meta-analysis. Random effect model for analysis expressed as 95% CI. The forest plot generated for all the different outcomes was used to assess the heterogeneity. We specifically used Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[10] The details of heterogeneity analysis have been elaborated elsewhere.[9]

Grading of results is an important as it helps us to understand the quality of the results generated in a meta-analysis. After all, any meta-analysis can be as good as the quality of RCTs used in the analysis. The grading/certainty of the evidence of some of the major secondary outcomes and primary outcomes in this meta-analysis was done using Grades of Recommendation, Assessment, Development and Evaluation approach.[11] The details have been elaborated elsewhere.[7] Publication bias was assessed by plotting the Funnel plot.[11,12] The details of how the Funnel plots were plotted have been elaborated elsewhere.[9] Funnel plots drawn have been elaborated in Supplementary Figure 2. Table 1 was generated using the GRADE software (https://gdt.gradepro.org/app/), which highlights the grading of key outcomes. Since ethical approval was already taken for the all the RCTs which were included in this meta-analysis and no new patients were evaluated here, there was no need for separate ethical approval for this meta-analysis.

Results

Eight duplicate articles were removed from the initial set of 23 articles found after initial search [Figure 1]. Further, the screening of titles, abstracts, and full texts reduced our search down to six studies which were evaluated in detail [Figure 1]. Data from four trials involving 718 people with T2DM which fulfilled all criteria were analysed.[5,6,13,14] The study published by Yang *et al.*[2] was excluded as it was a phase 2 pharmacodynamic and pharmacokinetic assessment study of 8 weeks duration only. The study by Cai *et al.*[15] was excluded from the analysis as it was the only study to evaluate peg-loxenatide 300 mcg/week with weight loss and not glycaemic control (HbA1c reduction) being the primary treatment outcome. The duration of the blinded or closely followed-up phase of the study in the trials by Chen *et al.*,[5] Gao *et al.*,[6] Shuai *et al.*,[13] and Li *et al.*[14] was 12 weeks, 24 weeks, 24 weeks, and 12 weeks, respectively. Data from this blinded or closely followed-up phase were analysed in this meta-analysis. The studies by Gao *et al.*[6] and Shuai *et al.*[13] also collected data on glycaemic durability and safety at 52 weeks of passive follow-up as a part of post-study safety follow-up. Since this was a single-arm phase of the study, the 52-week data could not be analysed in this meta-analysis.

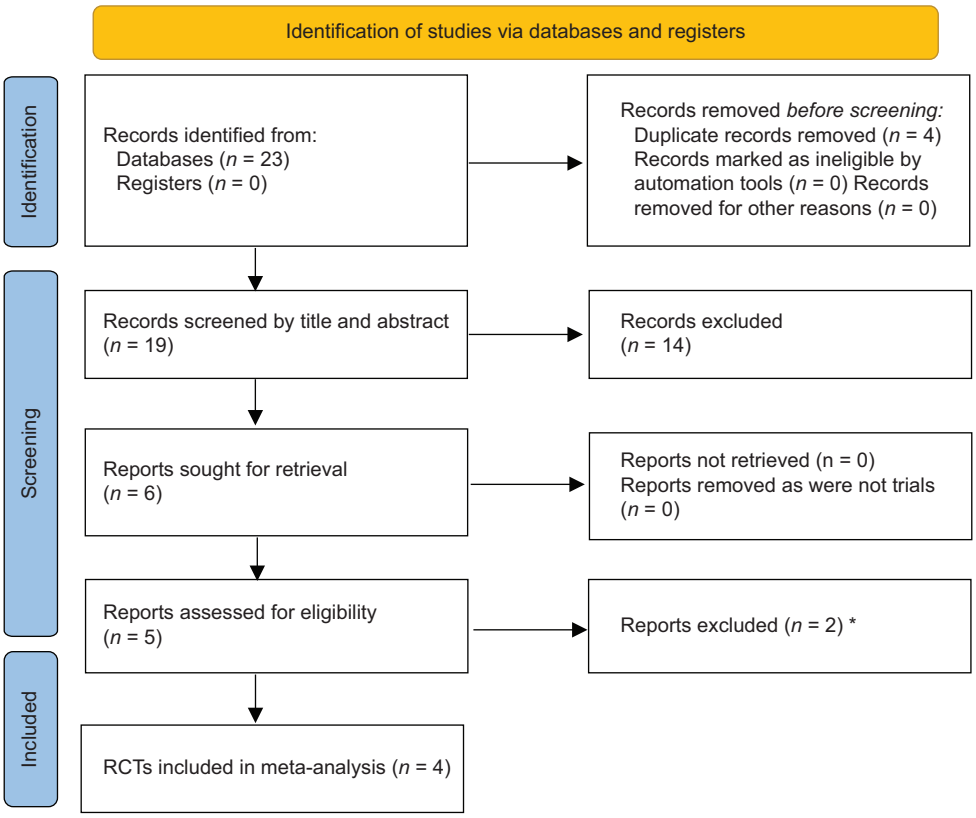

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis

Table 1: Summary of findings of the key outcomes of this meta-analysis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	Risk with PEG-Lox 100			
HbA1c	The mean HbA1c was 8.48%	MD 0.95 mmol/L lower (1.19 lower to 0.71 lower)	-	678 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
HbA1c <6.5%	63 per 1,000	187 per 1,000 (120 to 279)	OR 3.45 (2.05 to 5.81)	678 (3 RCTs)	⊕⊕⊕⊕ High
TAEs	460 per 1,000	470 per 1,000 (393 to 546)	OR 1.04 (0.76 to 1.41)	685 (3 RCTs)	⊕⊕⊕⊕ High
Anorexia	12 per 1,000	9 per 1,000 (2 to 38)	OR 0.78 (0.18 to 3.28)	685 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Nausea	6 per 1,000	17 per 1,000 (3 to 80)	OR 2.87 (0.56 to 14.72)	685 (3 RCTs)	⊕⊕⊕⊕ High
Outcomes	**Risk with Placebo**	**Risk with PEG-Lox 200**	**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**
HbA1c	The mean HbA1c was 8.48%	MD 1.15 mmol/L lower (1.47 lower to 0.82 lower)	-	662 (3 RCTs)	⊕⊕⊕◯ Moderate[b]
HbA1c <6.5%	63 per 1,000	248 per 1,000 (165 to 355)	OR 4.95 (2.97 to 8.27)	662 (3 RCTs)	⊕⊕⊕⊕ High
TAEs	460 per 1,000	492 per 1,000 (416 to 568)	OR 1.13 (0.83 to 1.53)	671 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Anorexia	12 per 1,000	44 per 1,000 (14 to 123)	OR 3.85 (1.24 to 11.88)	671 (3 RCTs)	⊕⊕⊕⊕ High
Nausea	6 per 1,000	47 per 1,000 (11 to 176)	OR 16.85 (3.89 to 72.92)	671 (3 RCTs)	⊕⊕⊕⊕ High

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); CI: confidence interval; MD: mean difference; OR: odds ratio; PEG-Lox 100: polyethylene glycol loxenatide at 100 mcg/week; PEG-Lox 200: polyethylene glycol loxenatide at 200 mcg/week; HbA1c: glycated haemoglobin; [a]. Funnel plot is suggestive of presence of most of the studies outside the plot; hence, it is likely that significant publication bias is present. [b]. Considerable heterogeneity present as I^2 >90%

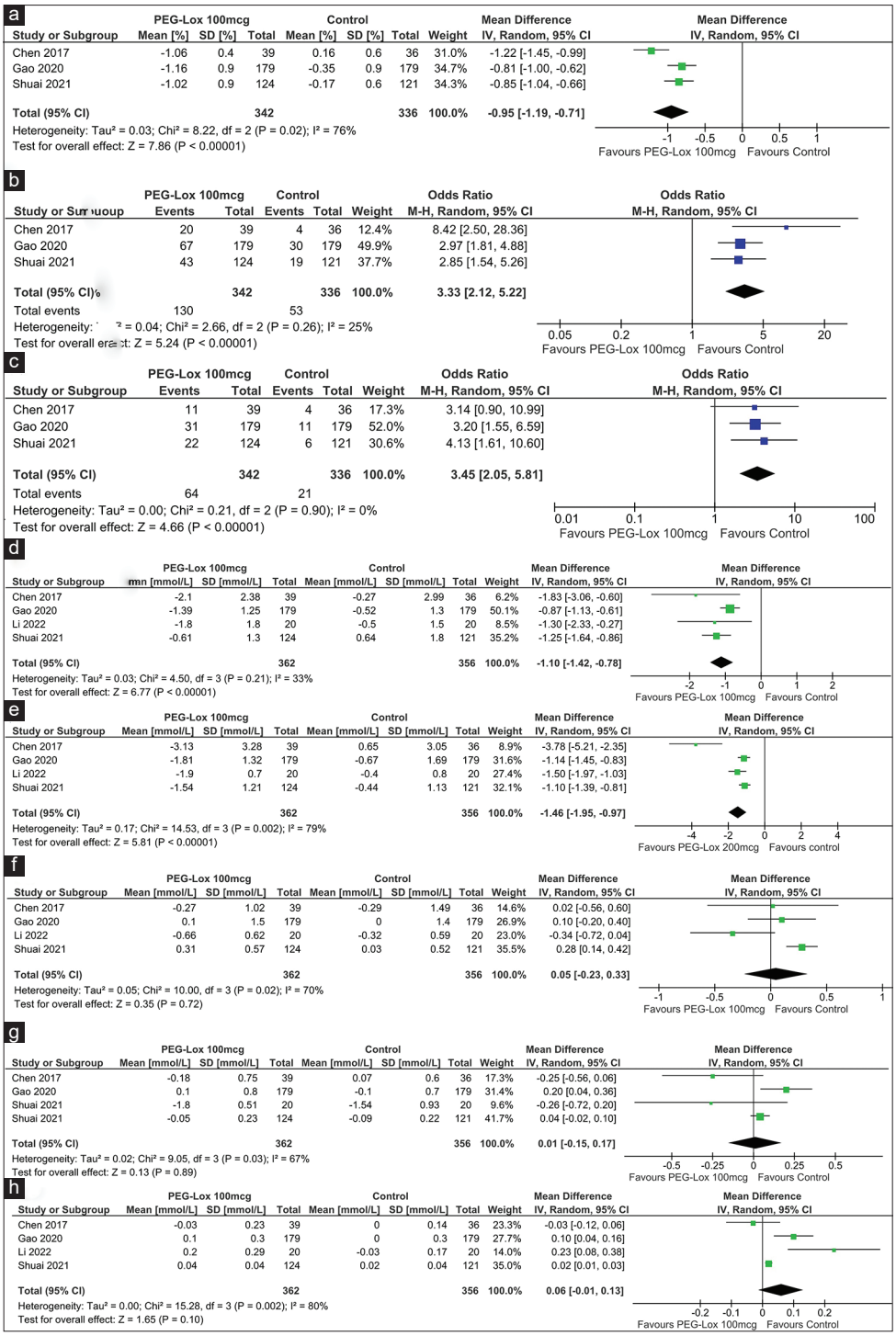

Figure 2: Forest plot highlighting the impact of peg-loxenatide 100 mcg/week as compared to placebo on (a) HbA1c, (b) people achieving HbA1c <7%, (c) people achieving HbA1c <6.5%, (d) fasting glucose, (e): 2 hour post-prandial glucose, (f): serum triglycerides, (g): serum LDL-cholesterol, and (h): serum HDL-cholesterol

Patient characteristics from the different RCTs in this meta-analysis are elaborated in Table 2.

Risk of bias in the included studies

Supplementary Figure 1a, Supplementary Figure 1b, and Supplementary Table 1 elaborate on the risk of bias. Random sequence generation, attrition bias, and reporting bias were at low risk in all the four studies (100%). Allocation concealment bias, performance bias, and detection bias were at low risk in three out of four studies (75%). Sources of funding, especially pharmaceutical industry funding, one or more authors from the pharmaceutical organization involved in the development of the drug, involvement of pharmaceutical organizations in data analysis and manuscript preparation, and conflict of interests

Table 2: Patient characteristics of the different randomized controlled trials evaluated in this meta-analysis

	Chen *et al*.[4]		Gao *et al*.[6]		Li *et al*.[14]		Shuai *et al*.[13]	
	PEG-Lox100 Group	Control Group	PEG-Lox100 Group	Control Group	PEG-Lox100 Group	Control Group	PEG-Lox100 Group	Control Group
Age (years)	52.6±8.4	53.5±10.2	53.6±10.5	52.3±10.7	63.29±1.27	64.23±1.31	50.5±10.4	51.5±10.9
Males	22 (53.66%)	26 (68.42%)	102 (57%)	98 (54.7%)	10 (50%)	10 (50%)	83 (65.9%)	88 (72.7%)
Disease duration (months)	53±77	77.5±95.0	52±40	56±41	-	-	12±11	20±17
BMI (kg/m^2)	27.2±4.5	27.2±3.6	26.0±3.5	26.9±3.9	28.19±3.23	28.26±3.11	27.0±3.7	26.3±3.4
SBP (mm Hg)	128±11	130±14	-	-	-	-	-	-
DBP (mm Hg)	78.1±9.4	77.8±9.0	-	-	-	-	-	-
Baseline HbA1c (%)	8.28±1.05	8.23±0.88	8.5±0.9	8.6±0.9	-	-	8.5±0.9	8.6±1.0
Fasting glucose (mmol/L)	9.47±2.52	9.54±2.42	-	-	6.2±1.8	6.4±1.5	9.06±2.11	9.91±2.54
2 h post-prandial glucose (mmol/L)	15.9±4.3	16.1±3.7	-	-	7.3±0.6	7.2±0.5	15.57±3.69	16.56±4.05
LDL-C (mmol/L)	3.02±0.80	2.98±0.85	-	-	4.52±0.71	4.51±1.42	-	-

All values have been expressed as mean±standard deviation; PEG-Lox100: polyethylene glycol loxenatide at 100 mcg/week dose; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycated haemoglobin

were looked into the "other bias" section. Other bias was at high risk in three out of the four studies (75%).

Effect of peg-loxenatide on primary and secondary outcomes

Data from three studies (678 patients) were analysed to determine the effect of peg-loxenatide 100 mcg/week (PEG-Lox100) on HbA1c and the percentage of people achieving HbA1c <7% and 6.5% after 12–24 weeks of treatment. Patients receiving PEG-Lox100 had significantly lower HbA1c [MD -0.95% (95% CI: -1.19 to -0.71); $P < 0.01$; I^2 = 76% (moderate heterogeneity (MH)); Figure 2a], compared to placebo. Significantly higher number of patients on PEG-Lox100 achieved HbA1c <7% [odds ratio (OR) 3.33 (95% CI: 2.12–5.22); $P < 0.01$; $I^2 = 25\%$ (low heterogeneity (LH)); Figure 2b] and HbA1c <6.5% [OR 3.45 (95% CI: 2.05–5.81); $P < 0.01$; $I^2 = 0\%$ (LH); Figure 2c] at the end of study as compared to placebo.

Data from four studies (718 patients) were analysed to determine the effect of PEG-Lox100 on FPG, PPG, serum triglycerides, LDL-cholesterol, and HDL-cholesterol. Patients receiving PEG-Lox100 had significantly lower FPG [MD -1.10 mmol/L (95% CI: -1.42 to -0.78); $P < 0.01$; I^2 = 33% (LH); Figure 2d] and PPG [MD -1.46 mmol/L (95% CI: -1.95 to -0.97); $P < 0.01$; I^2 = 79% (MH)S; Figure 2e] as compared to placebo. Changes in serum triglycerides [MD 0.05 mmol/L (95% CI: -0.23 to 0.33); $P = 0.72$; $I^2 = 72\%$ (MH); Figure 2f], LDL-cholesterol [MD 0.01 mmol/L (95% CI: -0.15 to 0.17); P = 0.89; $I^2 = 67\%$ (MH); Figure 2g], and HDL-cholesterol [MD 0.06 mmol/L (95% CI: -0.01 to 0.13); $P = 0.10$; $I^2 = 80\%$ (MH); Figure 2h] were comparable in patients receiving PEG-Lox100 as compared to placebo.

Data from three studies (662 patients) were analysed to determine the effect of the higher-dose peg-loxenatide 200 mcg/week (PEG-Lox200) on HbA1c, percentage of people achieving HbA1c <7% and 6.5%, FPG, PPG, serum triglycerides, LDL-cholesterol, and HDL-cholesterol after 12–24 weeks of treatment. Patients receiving PEG-Lox200 had significantly lower HbA1c [MD -1.15% (95% CI: -1.47 to -0.82); $P < 0.01$; I^2 = 90% (considerable heterogeneity (CH)); Figure 3a], FPG [MD -1.43 mmol/L (95% CI: -2.06–-0.80); $P < 0.01$; I^2 = 78% (MH); Figure 3d], and PPG [MD -2.16 mmol/L (95% CI: -3.20 to -1.13); $P < 0.01$; $I^2 = 90\%$ (CH); Figure 3e] as compared to placebo. A significantly higher number of patients on PEG-Lox200 achieved HbA1c <7% [OR 4.65 (95% CI: 2.71–7.97); $P < 0.01$; $I^2 = 44\%$ (MH); Figure 3b] and HbA1c <6.5% [OR 4.95 (95% CI: 2.97–8.27); $P < 0.01$; $I^2 = 0\%$ (LH); Figure 3c] at the end of study as compared to placebo

Changes in serum triglycerides [MD 0.05 mmol/L (95% CI: -0.05 to 0.14); P = 0.35; I^2 = 0% (LH); Figure 3f], LDL-cholesterol [MD -0.03 mmol/L (95% CI: -0.33 to 0.26); P = 0.83; I^2 = 92% (CH); Figure 3g], and HDL-cholesterol [MD -0.00 mmol/L (95% CI: -0.01 to 0.01); $P = 0.90$; $I^2 = 0\%$ (LH); Figure 3h] were comparable in patients receiving PEG-Lox200 as compared to placebo.

Data from three studies (643 patients; Gao *et al*.,[6] Li *et al*.[14] and Shuai *et al*.[13]) were analysed to determine the effect of peg-loxenatide 100 mcg/week on body weight. Changes in body weight with peg-loxenatide 100 mcg/week [MD -1.52 kg (95% CI: -4.98 to 1.95); $P = 0.39$; $I^2 = 88\%$ (MH)] were similar to that of placebo. Data from two studies (591 patients; Gao *et al*.[6] and Shuai *et al*.[13]) were analysed to find out the impact of peg-loxenatide 200 mcg/week on body weight. Changes in body weight with peg-loxenatide 200 mcg/week [MD 0.16 kg (95% CI: -0.08 to 0.40); $P = 0.18$; $I^2 = 0\%$ (LH)] were similar to that of placebo.

Data from three studies (678 patients; Chen *et al*.,[5] Gao *et al*.,[6] and Shuai *et al*.[13]) were analysed to determine the effect of peg-loxenatide 100 mcg/week on systolic (SBP) and diastolic blood pressure (DBP). Changes in SBP [MD 0.59 mm Hg (95% CI: -0.00 to 1.18); $P = 0.06$; $I^2 = 0\%$ (LH)] and DBP [MD -0.34 mm Hg (95% CI: -1.98 to 1.30); P = 0.69;

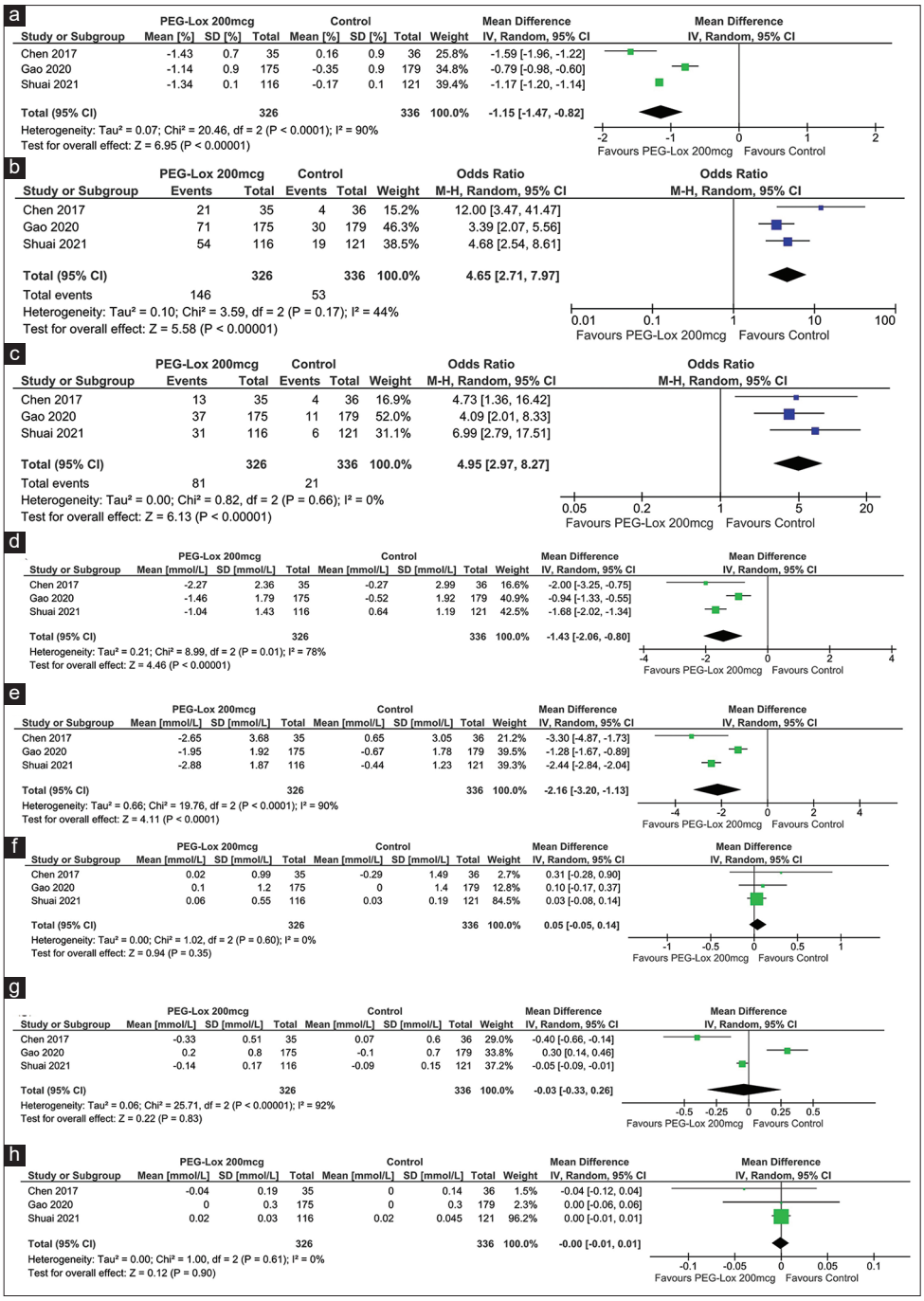

Figure 3: Forest plot highlighting the impact of peg-loxenatide 200 mcg/week as compared to placebo on (a) HbA1c, (b) people achieving HbA1c <7%, (c) people achieving HbA1c <6.5%, (d) fasting glucose, (e): 2 hour post-prandial glucose, (f): serum triglycerides, (g): serum LDL-cholesterol, and (h): serum HDL-cholesterol

I^2 = 70% (MH)] with peg-loxenatide 100 mcg/week were similar to that of placebo.

Data from three studies (662 patients; Chen *et al.*,[5] Gao *et al.*,[6] and Shuai *et al.*[13]) were analysed to determine the effect of peg-loxenatide 200 mcg/week on SBP and DBP. Changes in SBP [MD 1.09 mm Hg (95% CI: -1.70 to 3.89); P = 0.44; I^2 = 78% (MH)] and DBP [MD 0.15 mm Hg (95% CI: -1.94 to 2.25); P = 0.88; I^2 = 82% (MH)] with peg-loxenatide 200 mcg/week were similar to that of placebo.

Safety

Data from three studies (685 patients) were analysed to determine the effect of PEG-Lox100 on the burden of adverse events [(total adverse events (TAEs) and severe adverse events (SAEs)], nausea, vomiting, diarrhoea, and anorexia over 12–24 weeks of treatment. The occurrences of TAEs [RR 1.04 (95% CI: 0.76–1.41); P = 0.81; I^2 = 0% (LH); Figure 4a], SAEs [RR 1.20 (95% CI: 0.56–2.58); P = 0.63; I^2 = 0% (LH); Figure 4b], nausea [RR 2.87 (95% CI: 0.56–14.72); P = 0.21;

I^2 = 10% (LH); Figure 4c], vomiting [RR 4.73 (95% CI: 0.53–41.88); P = 0.16; I^2 = 0% (LH); Figure 4d], diarrhoea [RR 1.12 (95% CI: 0.19–6.45); P = 0.90; I^2 = 50% (MH); Figure 4e], and anorexia [RR 0.78 (95% CI: 0.18–3.28); P = 0.73; I^2 = 0% (LH); Figure 4f] were comparable among patients receiving PEG-Lox100 as compared to placebo.

Data from three studies (671 patients) were analysed to determine the effect of PEG-Lox200 on the occurrence of TAEs, SAEs, nausea, vomiting, diarrhoea, and anorexia over 12–24 weeks of treatment. The occurrences of TAEs [RR 1.13 (95% CI: 0.83–1.53); P = 0.44; I^2 = 0% (LH); Figure 5a], SAEs [RR 0.77 (95% CI: 0.24–2.44); P = 0.66; I^2 = 29% (LH); Figure 5b], and diarrhoea [RR 2.63 (95% CI: 0.83–8.38); P = 0.10; I^2 = 24% (LH); Figure 5e] were comparable among patients receiving PEG-Lox200 as compared to placebo.

The occurrences of nausea [RR 16.85 (95% CI: 3.89–72.92); P < 0.01; I^2 = 10% (LH); Figure 5c], vomiting [RR 15.90 (95% CI: 2.99–84.55); P < 0.01; I^2 = 0% (LH); Figure 5d], and anorexia [RR 3.85 (95% CI: 1.24–11.88); P = 0.02; I^2 = 0% (LH); Figure 5f] were significantly higher in patients receiving PEG-Lox200 as compared to placebo.

The occurrences of anti-peg-loxenatide antibodies were not increased in patients receiving standard-dose (100 mcg/week) [RR 1.76 (95% CI: 0.37–8.48); P = 0.48; I^2 = 0% (LH)] and high-dose (200 mcg/week) [RR 2.58 (95% CI:

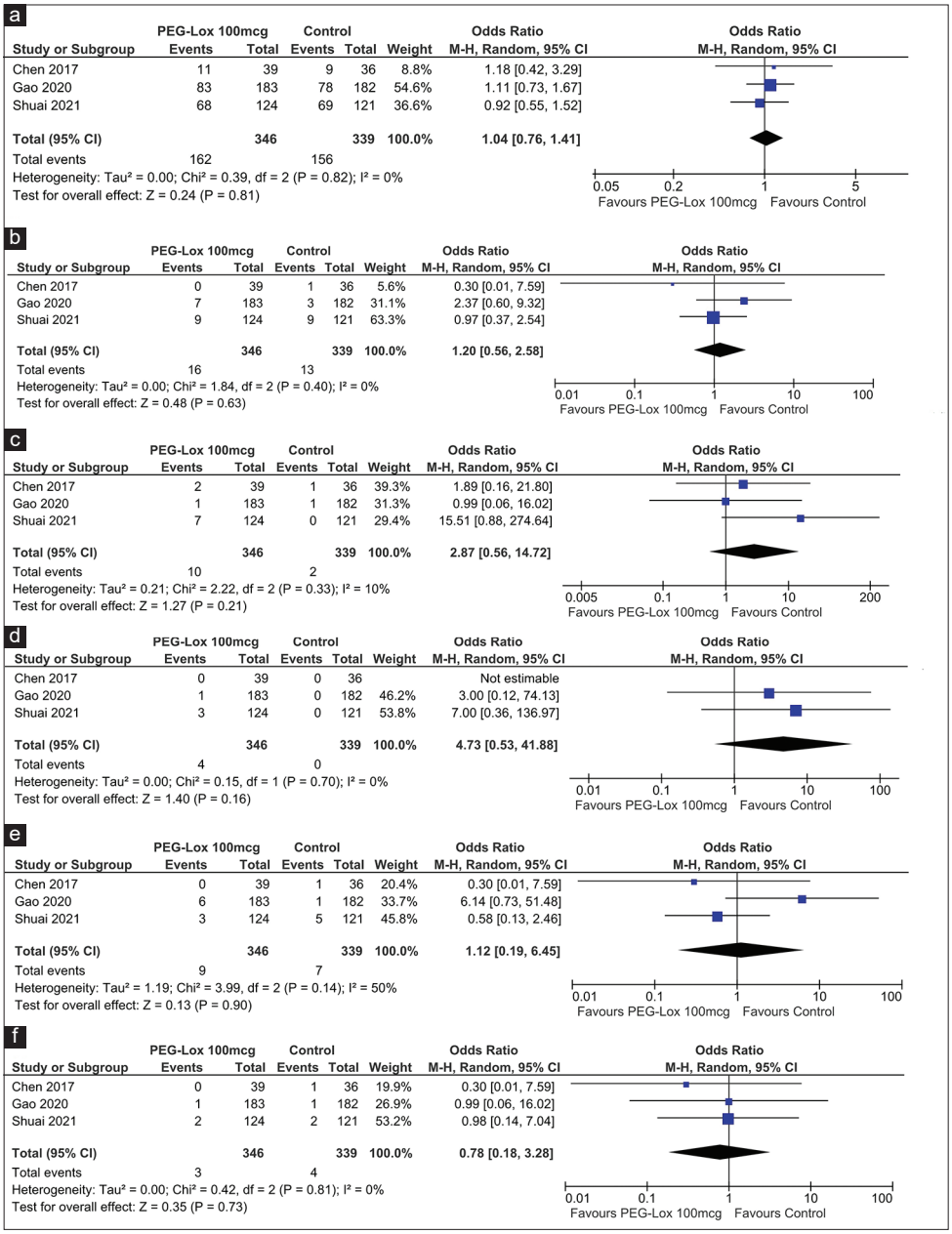

Figure 4: Forest plot highlighting the impact of peg-loxenatide 100 mcg/week as compared to placebo on (a) TAEs, (b) SAEs, (c) nausea, (d) vomiting, (e): diarrhoea, and (f): anorexia

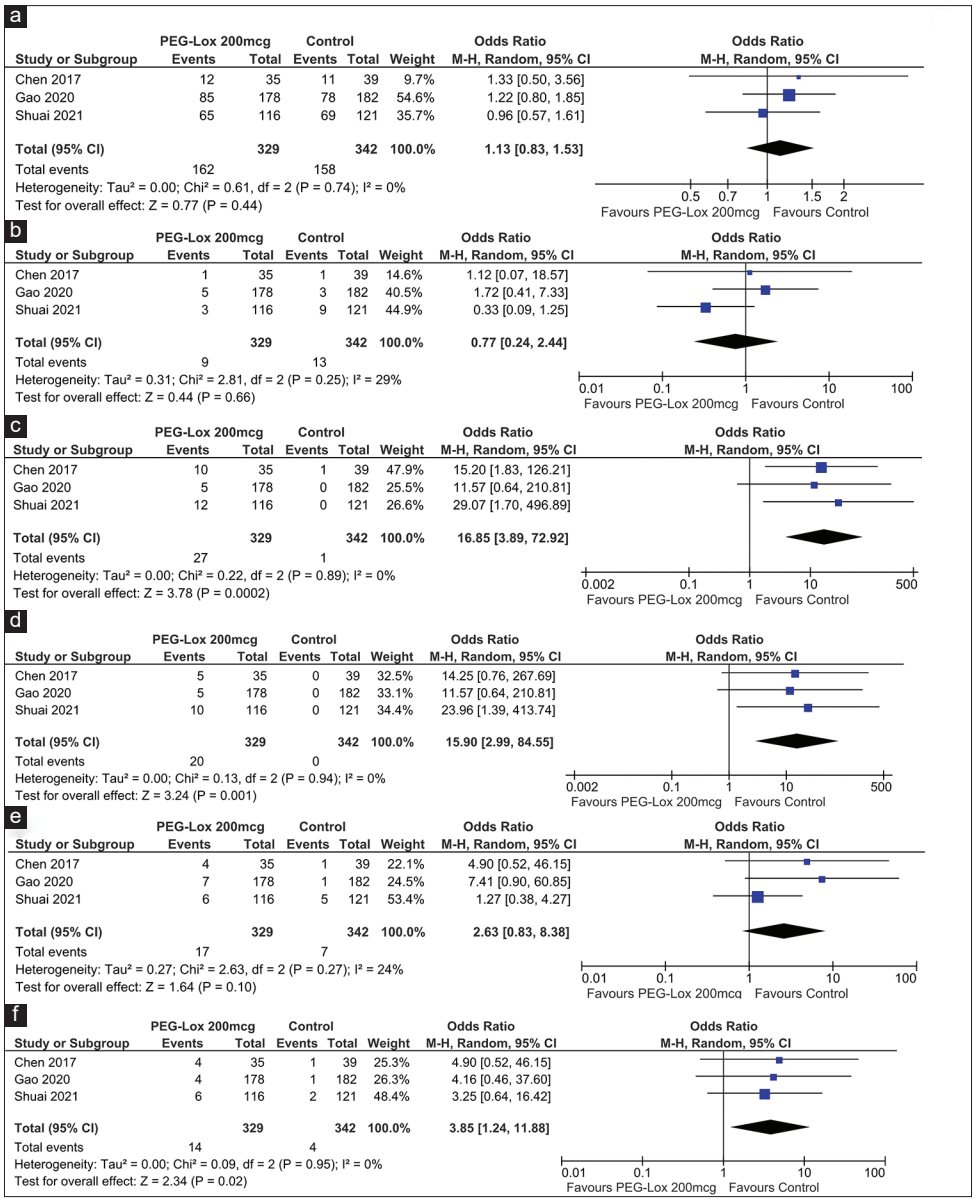

Figure 5: Forest plot highlighting the impact of peg-loxenatide 200 mcg/week as compared to placebo on (a) TAEs, (b) SAEs, (c) nausea, (d) vomiting, (e): diarrhoea, and (f): anorexia

0.51–13.13); $P = 0.25$; $I^2 = 8\%$ (LH)] peg-loxenatide. The summary of findings of the key outcomes of this study with peg-loxenatide 100 mcg/week and 200 mcg/week is elaborated in Table 1.

Peg-loxenatide 300 mcg/d as an antiobesity medicine

Only one open-labeled RCT (n = 156) having 16 weeks follow-up has compared peg-loxenatide 300 mcg/week head-to-head to metformin 1500 mg/d.[15] After 16 weeks, the documented weight loss was 7.52 kg (8.37%) and 2.96 kg (3.00%) with peg-loxenatide and metformin, respectively ($P < 0.01$).[2] At the end of the study, Hba1c reduction in the peg-loxenatide 300 mcg/week group [-1.22%; (95% CI: -1.38 to -1.06)] and the metformin 1500 mg/d group [-1.17%; (95% CI: -1.57, -1.34)] was similar ($P = 0.69$).[15] Gastro-intestinal (GI) side effects were significantly higher with peg-loxenatide 300 mg/week (24.0%) as compared to metformin group (17.3%).[15] Occurrences of hypoglycaemic events were similar with peg-loxenatide 300 mg/week [2.9% (3/104)] and metformin 1500 mg/d [.8% (2/52].[15]

Discussion

This is the first meta-analysis to highlight the efficacy and safety of standard-dose (100 mcg/week) and high-dose (200 mcg/week) PEG-Lox in the management of T2DM. Over 12–24 weeks of clinical use, both standard-dose and high-dose PEG-Lox had good glycaemic efficacy as compared to placebo. The mean HbA1c reduction (MD: -1.15% vs -0.95%) and percentage of people achieving HbA1c <7% (OR: 4.65 vs 3.33) and <6.5% (OR: 4.95 vs 3.45) were marginally better with high-dose PEG-Lox as compared to standard-dose PEG-Lox. However, this

increased glycaemic efficacy with high-dose PEG-Lox came with the associated increased GI problems of significantly higher nausea, vomiting, and anorexia, which was not noted with standard-dose peg-loxenatide.

The mean HbA1c reduction with oral and injectable semaglutide was noted to be -1.04% [95% CI (-1.26 - -0.83)] and -1.03% [95% CI (-0.85 - -1.22)], respectively, as compared to placebo in two different meta-analyses.[16,17] In a meta-analysis involving 21 RCTs, the mean reduction in HbA1c with injection dulaglutide 1.5 mg/week was noted to be -0.55% [95% CI (-0.39 to -0.70)].[18] The mean HbA1c reduction of −1.10% [95% CI (−1.13 to −1.07)] was noted with injection liraglutide 1.2 mg/day as compared to placebo in a meta-analysis involving data from nine RCTs.[19] Hence, glycaemic efficacy of PEG-Lox appears to be comparable to that of other available GLP1RAs in clinical practice. This meta-analysis highlights that weight loss is negligible with PEG-Lox at 100 mcg/week or 200 mcg/week dose, which is in stark contrast to other peer long-acting GLP1RAs like semaglutide and liraglutide. The reason for lack of weight loss needs further evaluation. Studies have shown that GLP-1 analogues like PEG-Lox improve endothelial cell function indicators in people living with diabetes through alterations of gut microbiota like Eubacterium ramulus ATCC 29099, Acinetobacter, and Bacteroides-faecis.[5]

It is important to highlight that all the current available RCTs analysed in this meta-analysis have compared PEG-Lox with placebo. Only one RCT has been recently published comparing PEG-Lox head-to-head with metformin.[15] However, it was not included in our analysis as it used PEG-Lox at 300 mcg/week dose with weight loss and not glycaemic efficacy being the primary outcome. However, this trial does give us additional vital information regarding this molecule. The HbA1c reduction with PEG-Lox 300 mcg/week was -1.17%, which is similar to that noted with PEG-Lox 200 mcg/d and 100 mcg/d in our meta-analysis (-1.15% and 0.95%, respectively). Hence, glycaemic efficacy does not increase significantly beyond 100 mcg/week dose. The greater weight loss with PEG-Lox 300 mcg/week comes at a cost of significantly higher occurrence of GI side effects. The occurrence of GI side effects with PEG-Lox 100 mcg/week was similar to that with placebo as noted in our meta-analysis. However, even when compared to metformin 1500 mg/d (which is a pretty high dose of metformin and per se linked with significant GI side effects), PEG-Lox still had further significantly higher occurrence of GI side effects in the RCT by Cai *et al*.[15] There is a general consensus that weight loss and GI side effects often go in sync with regard to GLP1RA.[20]

Hence, there still remains the need for urgent RCTs comparing the glycaemic efficacy and durability of PEG-Lox (100 mcg/week and 200 mcg/week) with those of other established antidiabetes medications like peer GLP1RAs, sodium-glucose contransporters-2 (SGLT2) inhibitors, sulfonylureas, and insulin. Some of the other unique attributes of PEG-Lox include the fact that being the first GLP1RA to be developed in the "east," and with more clinical data likely to be published in the next few years, this molecule should be able to spread across the globe from China. PEG-Lox also has the potential to make GLP1RA therapy affordable, which is currently out of reach for large sections of the global population.

To conclude, it may be said that PEG-Lox injections at 100 mcg/week may be the most appropriate dose for clinical use as it is associated with good glycaemic efficacy with minimal GI side effects. High-dose PEG-loxenatide (200 mcg/week) has only marginal additional glycaemic efficacy, having the limitation of significantly higher occurrence of GI side effects.

Highlights

- The mean HbA1C reduction is -0.95% with standard-dose peg-loxenatide (100 mcg/week).
- The mean HbA1C reduction is -1.15% with high-dose peg-loxenatide (200 mcg/week).
- Gastro-intestinal side effects are significantly higher with high-dose peg-loxenatide.
- Weight loss is not seen with peg-loxenatide.

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Conflicts of interest

There are no conflicts of interest.

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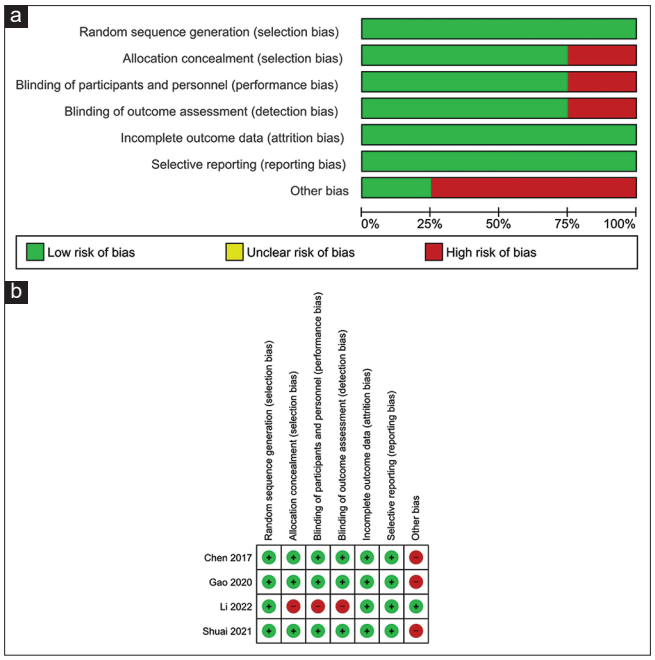
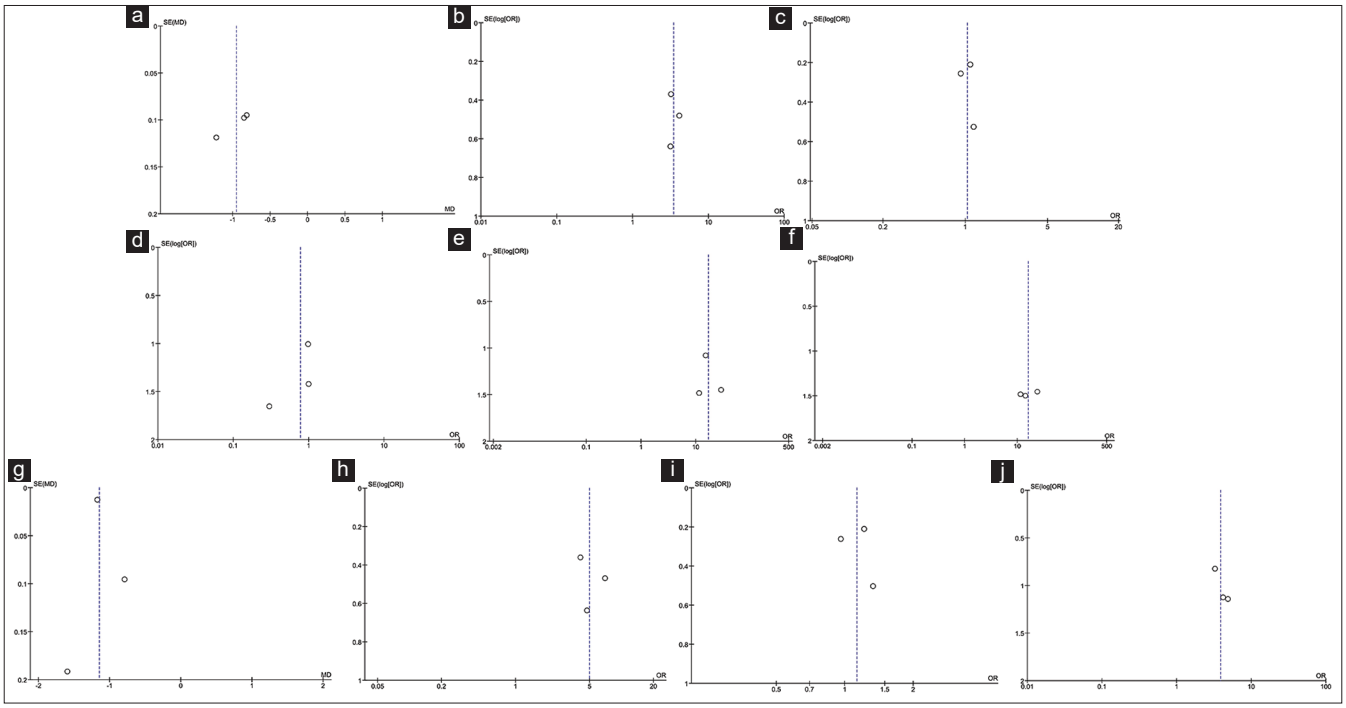
Supplementary Table 1: Risk of bias assessment table

Chen 2017	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Multicenteric randomized double-blind parallel placebo controlled clinical trial
Allocation Concealment (Selection Bias)	Low Risk	Central dynamic block randomization was done
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Yes, double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Yes, double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low RIsk	Data from 108 patients from the initially randomized 120 patients were analyzed. Hence attrition rate was 12/120 (10%). An attrition rate of >15% was considered to he high
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	This study was supported financially by Hansoh Pharmaceutical (Jiangsu, China). Hansoh Pharmaceutical provided English-language editing services
Gao 2020	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Multicentric, randomized, double-blind, placebo-controlled trial
Allocation Concealment (Selection Bias)	Low Risk	Randomization and drug container assignment were managed using a central randomization system.
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	573 patients were randomized of which data from 533 patients were analysed. Hence attrition rate was 40/573 (6.9%)
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The study was funded by China Jiangsu Hansoh Pharmaceutical Group Co., Ltd (Hansoh Pharma).
Li 2022	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Open labelled study
Allocation Concealment (Selection Bias)	High risk	Open labelled study, hence allocation concealment not done
Blinding Of Participants & Personel (Performance Bias)	High Risk	Open labelled study
Blinding Of Outcome Assessment (Detection Bias)	High Risk	Open labelled study
Incomplete Outcome Data (Attrition Bias)	Low Risk	All 40 patients randomly allocated to study and control group completed the study.
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	Low Risk	Nothing significant to report
Shuai 2021	**Risk of Bias**	**Author Judgement**
Random Sequence Generation (Selection Bias)	Low Risk	Multicenteric, randomized, double blinded placebo-controlled clinical trial
Allocation Concealment (Selection Bias)	Low risk	Subjects were randomized using the PLAN procedure in SAS software and stratified by baseline HbA1c
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	369 out of the 406 patients selected for randomization completed the study. Hence attrition rate was less than 15%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	This study was funded by Jiangsu Hansoh Pharmaceutical Group Co., Ltd. (Hansoh Pharma). The authors thank all the investigators and subjects. Yale Duan contributed to medical writing, and Ning Du provided editorial support, who were all from Hansoh Pharma



Supplementary Figure 1: (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (b) Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Supplementary Figure 2: Funnel plot assessing the publication bias for key outcomes of this meta-analysis (a) HbA1c reduction with peg-loxenatide 100mcg/week; (b) HbA1c <6.5% with peg-loxenatide 100mcg/week; (c): Treatment emergent adverse events (TAEs) with peg-loxenatide 100mcg/week; (d): Anorexia with peg-loxenatide 100mcg/week; (e): Nausea with peg-loxenatide 100mcg/week; (f): Vomiting with peg-loxenatide 100mcg/week; (g): HbA1c reduction with peg-loxenatide 200mcg/week; (h): HbA1c<6.5% with peg-loxenatide 200mcg/week; (i): TAEs with peg-loxenatide 200mcg/week; (j): Anorexia with peg-loxenatide 200mcg/week