REVIEW ARTICLE

Effectiveness and safety of semaglutide in overweight/obese adults with or without type 2 diabetes: A systematic review and meta-analysis

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Background: The objective of the study was to systematically evaluate the efficacy and safety of semaglutide in overweight or obese adults with or without type 2 diabetes. **Materials and Methods:** The study, registered with PROSPERO (CRD42023450979), was designed as a systematic review and meta-analysis. Using a combination of subject matter and free words, a comprehensive search of Embase, PubMed, and Cochrane Library databases was performed to identify randomized controlled trials of semaglutide in overweight or obese adults with or without Type 2 diabetes mellitus from January 1, 2020, to July 14, 2023. The primary outcomes were the changes in body weight and adverse drug reaction (ADR). Random or fixed effects models were used in meta-analysis, pooling data as relative risks (RRs) or mean difference (MD) with 95% confidence intervals (CIs). Cochrane Collaboration's Risk of Bias tool was used to assess quality. Meta-analysis was performed using RevMan 5.3. **Results:** A total of 2490 publications were retrieved. Fifteen publications were finally included, totaling 6984 overweight or obese adult patients. Meta-analysis showed that compared with the control group, the semaglutide group was reduced more significantly in body weight (MD = −7.49, 95% CI [−9.92, −5.07], $P < 0.001$), body mass index (MD = −3.35, 95% CI [−4.79, −1.92], $P < 0.001$), waist circumference (MD = −7.26, 95% CI [−9.94, −4.58], $P < 0.001$), as well as glycosylated hemoglobin (RR = −0.66, 95% CI [−1.07, −0.25], $P = 0.002$), fasting blood glucose values (RR = −4.81, 95% CI [−7.03, −2.60], $P < 0.001$), and systolic blood pressure (RR = −3.37, 95% CI [−5.32, −1.42], $P < 0.001$), and the proportion of patients who lost > 5%, 10%, 15%, and 20% of their overall body weight, respectively (RR = 3.19, 95% CI [1.89, 5.36], $P < 0.001$), (RR = 4.74, 95% CI [2.78, 8.11], $P < 0.001$), (RR = 6.17, 95% CI [3.88, 9.82], $P < 0.001$), and (RR = 9.14, 95% CI [6.05, 13.80], $P < 0.001$) were also superior to the control group. Regarding safety, the incidence of total ADR in the semaglutide group was close to the placebo group. Still, gastrointestinal adverse effects such as nausea, vomiting, abdominal pain, and diarrhea were higher than those in the control group. **Conclusion:** Semaglutide can effectively lose weight in overweight or obese adults with or without diabetes, potentially providing cardiovascular benefits; however, gastrointestinal adverse should be closely monitored.

Key words: Efficacy, glucagon-like peptide 1, obesity, safety, semaglutide

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INTRODUCTION

Obesity and overweight are defined as abnormal or excessive fat accumulation that poses a health risk. Body mass index (BMI) is an indicator that is often used to judge obesity and overweight. BMI ≥25 kg/m^2 is defined as overweight, and BMI ≥30 kg/m^2 is described as obese.[1] In recent years, with the development of economic conditions and the continuous improvement of living standards, the phenomenon of being overweight or obese is becoming more and more acute. According

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to data, the number of obese people worldwide has tripled since 1975.[1] At present, China has the largest overweight or obese population of any country in the world, with 600 million. More than half of obese adults have multiple complications due to obesity.[2] Obesity and overweight are caused by many factors, mainly genetic, environmental, disease, and other factors. Obesity is closely related to various chronic conditions, such as cardiovascular disease, stroke, T2DM, nonalcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, and certain cancers (breast, prostate, colon, and rectal cancers), and the degree of risk increases with the increase of BMI, which can increase economic stress, seriously affect study, work, and life. People who are overweight are three times more likely to develop type 2 diabetes than those of average weight.

Generally, people control obesity through lifestyle interventions, but their effectiveness and durability vary from person to person.[3] Therefore, using medication-assisted therapy to control weight has become a choice for more obese and overweight people. As a new type of hypoglycemic drug, semaglutide belongs to the long-acting glucagon-like peptide-1 (GLP-1) receptor agonist, which can selectively bind and activate the GLP-1 receptor, stimulate the secretion of insulin by pancreatic islet B-cells, and inhibit the release of insulin, lower blood glucose; in addition, it has been shown that semaglutide can lose weight in adults with overweight or obesity.[4] Relevant analyses have concluded that semaglutide is more effective than other GLP-1 receptor agonists in improving glycemia and other cardiometabolic risk factors in patients with T2DM.[5] The guidelines suggest overweight and obese adults with insufficiently effective lifestyle interventions can add semaglutide 2.4 mg for long-term intervention.[6] Although relevant meta-analysis has been published in recent years to analyze the efficacy and safety of semaglutide for weight loss in obese adults, there were incomprehensive and lacked pooled comparisons evaluating the effectiveness of semaglutide in obese or overweight adults with or without diabetes mellitus versus placebo or other glucose-lowering medications in controlling body weight.[7,8] Therefore, this article collects and analyzes the most recent clinical data on semaglutide in weight loss to provide a more comprehensive theoretical basis for the rational clinical use of semaglutide in obese or overweight adults with or without diabetes mellitus.

METHODS

Search strategy

A comprehensive systematic search of Cochrane Library, Embase, and PubMed was performed from January 1, 2020, to July 14, 2023. The investigation was conducted by combining subject terms with free words, and the English search terms included "obesity, obese, overweight, overweight, weight gain, adiposity, Rybelsus, semaglutide, wegovy, ozempic, NN9934, NN9935, NN9936, GLP-1 receptor agonist, GLP-1RA, glucagon-like peptide 1, glucagon-like peptide 1 receptor agonist" [Appendix 1 for search strategies].

Inclusion and exclusion criteria

Inclusion criteria

(1) Randomized controlled trials (RCTs); (2) overweight or obese adult patients (BMI ≥24 kg/m^2),[9] included with and without diabetes; (3) the experimental group: semaglutide, the control group: placebo or other glucose-lowering medication; and (4) English literature.

Exclusion criteria

(1) Repeated studies published multiple times; (2) studies that did not report outcome; and (3) studies with incomplete information reporting or inability to extract data.

Data extraction

Literature screening, data extraction, and quality assessment were conducted independently by two reviewers strictly according to the inclusion and exclusion criteria, and any conflicts were resolved by a discussion or arbitration by a third reviewer. The following information was extracted from the final included studies: first author, years of publication, presence or without T2DM, number of cases, intervention, age, BMI, duration of treatment, and outcome indicators. Primary outcome indicators: body weight, the proportion of patients with weight loss of >5%, 10%, 15%, and 20% overall, respectively, BMI and waist circumference. Secondary outcome indicators: systolic blood pressure (SBP), diastolic blood pressure (DBP), glycosylated hemoglobin A1c, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), total adverse drug reaction (ADR), nausea, vomiting, abdominal pain, and diarrhea.

Methodological quality evaluation

The risk of bias in the studies was evaluated by two independent reviewers using the Cochrane Risk of Bias tool for RCT. The evaluation included whether the allocation was randomized, whether the allocation was hidden, whether blinding was used, whether the outcome data were complete, whether there was selective reporting of study results and other biases. Any conflicts were resolved by a discussion or arbitration by a third reviewer.

Data synthesis and analysis

Meta analysis was performed using RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration,

Copenhagen, Denmark) Mean difference (MD) was used for continuous variables, and risk ratio (RR) was used for dichotomous variables to express the combined effect size; 95% confidence interval (CI) was used for interval estimation. $P < 0.05$ was considered statistically significant. Statistical heterogeneity between trials was assessed using the I^2 statistics, and when $I^2 < 50\%$ and $P > 0.05$ indicated less or no heterogeneity, the fixed-effects model was used for combined analysis. On the contrary, a random effects model was used. Funnel plots were done for the included literature to observe publication bias.

RESULTS

Literature screening process and results

The search yielded 2490 articles after rigorous screening, and 15 RCTs[6-20] were finally included in the review, totaling 6984 patients. The highest sample size is 1748, and the lowest sample size is 32. The literature screening process is shown in Figure 1, and the basic information of the included studies is shown in Table 1.

Methodological quality assessment of the included studies

Fifteen studies reported random sequence generation,[10-24] 10 studies provided information on allocation concealment,[12-19,22,23] 11 studies used blind methods,[12-19,21-23] 13 studies had a low bias of complete data,[10-17,19,21-24] and two trials had a low risk of other biases,[12,15] and the results of the quality assessment of the risk of bias is shown in Figure 2.

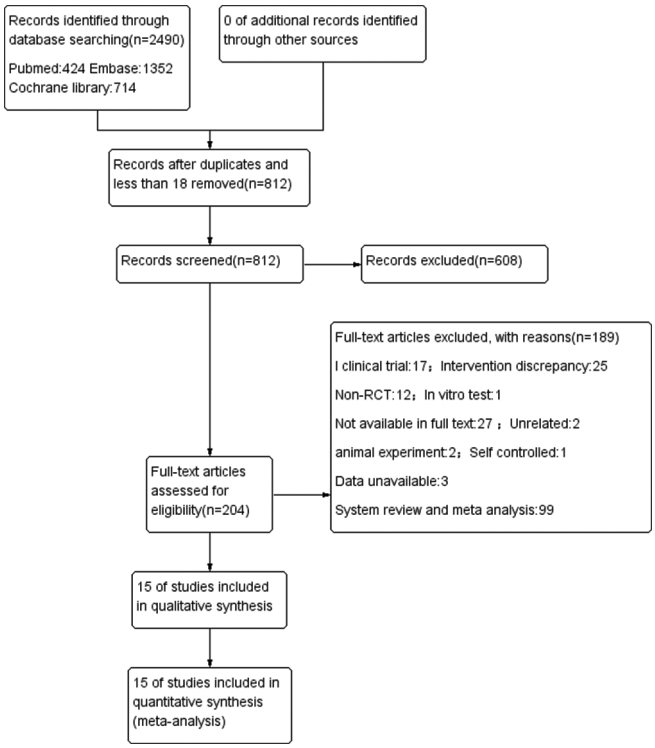

Figure 1: Literature screening process

Meta-analysis results

Efficacy indicators

Body weight

Ten RCTs[14-19,21-24] reported the value of patient's body weight reduction, and there was statistical heterogeneity among the studies ($P < 0.001$, $I^2 = 98\%$), so a random-effects model was chosen, and the results are shown in Figure 3. Compared with the control group, in the semaglutide group, more mean weight reduction was reported in all of the included trials (MD = −7.49, 95% CI [−9.92, −5.07], $P < 0.001$). Subgroup analysis showed that semaglutide led to more weight loss in overweight or obese patients without diabetes (MD = −11.41, 95% CI [−13.14, −9.68], $P < 0.001$), overweight or obese patients with diabetes (MD = −3.29, 95% CI [−4.78, −1.80], $P < 0.001$), or with or without diabetes overweight or obese patients (MD = −9.60, 95% CI [−11.44, −7.76], $P < 0.001$), and the difference was statistically significant. The results suggest semaglutide is superior to placebo or other hypoglycemic agents for weight reduction in overweight or obese adults with or without T2DM.

Percentage of weight >5%,10%,15%, and 20%

Seven RCTs[11,17-23] reported the proportion of patients with reductions more significant than 5%, 10%, 15%, and 20% of the overall population, respectively. There was statistically significant heterogeneity between studies ($P < 0.001$, $I^2 = 95\%$), so a random-effects model and subgroup analysis was performed. The results are shown in Figure 4. The results showed that there were more proportion reductions in the semaglutide group than in the control group, and the difference was statistically significant (RR = 4.82, 95% CI [3.46, 6.71]). The subgroup results showed that the proportion of patients with weight loss > 5%, 10%, 15%, and 20% of the overall body weight was significantly higher in the semaglutide group than in the control group (RR = 3.19, 95% CI [1.89, 5.36], $P < 0.001$), (RR = 4.74, 95% CI [2.78, 8.11], $P < 0.001$), (RR = 6.17, 95% CI [3.88, 9.82], $P < 0.001$), and (RR = 9.14, 95% CI [6.05, 13.80], $P < 0.001$), and the difference was statistically significant.

Body mass index

Five RCTs[14,15,17,18,22] reported the value of the patient's body weight reduction, and there was statistical heterogeneity among the studies ($P < 0.001$, $I^2 = 99\%$), so a random-effects model was chosen, and the results are shown in Figure 5. Compared with the control group, in the semaglutide group, more BMI reductions were reported in all of the included trials (MD = −3.35, 95% CI [−4.79, −1.92], $P < 0.001$). Subgroup analysis showed that semaglutide led to more BMI reduction in overweight or obese patients without diabetes mellitus (MD = −4.71, 95% CI [−5.03, −4.40], $P < 0.001$), overweight or obese patients with diabetes mellitus (MD = −1.79, 95% CI [−2.57, −1.00], $P < 0.001$), and the differences were statistically significant.

Table 1: Baseline characteristics of included studies

Author	T2DM	Stages	Sample size (treatment/control)	Therapeutic measures	Age (years)	Body weight (kg)	BMI (kg/m²)	Treatment course (W)	Outcome indicators
Capehorn *et al.*, 2020[10]	T2DM	III	290/287	Once-weekly semaglutide, 1.0 mg	60.1±10.5	96.6±21.0	33.7±6.6	30	⑱⑲⑳㉑㉒
				Once-daily liraglutide, 1.2 mg	58.9±10.0	97.2±21.7	33.7±7.0		
Buse *et al.*, 2020[11]	T2DM	NA	100/98	Oral semaglutide	58±10	85.8±15.4	31.0±5.4	52	②⑰⑱⑲⑳㉑㉓
				Sitagliptin, 100 mg	58±10	86.9±20.4	30.6±5.9		
McCrimmon *et al.*, 2020[12]	T2DM	IIIb	88/90	Once weekly semaglutide, 1.0 mg	57.8±9.9	89.0±18.2	32.6±6.4	52	⑦
				Once daily canagliflozin, 300 mg	58.6±10.1	87.6±18.2	32.3±5.5		
Yamada *et al.*, 2020[13]	T2DM	II/IIIa	48/49	Oral semaglutide, 14 mg	61±9	68.0±13.0	24.7±4.1	52	⑰⑱⑲㉑㉓
				Placebo	59±9	70.3±12.4	25.1±3.9		
Rubino *et al.*, 2021[14]	No	IIIa	535/268	Once weekly semaglutide, 2.4 mg	47±12	96.5±22.5	34.5±6.9	48	①⑥⑦⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓
				Placebo	46±12	95.4±22.7	34.1±7.1		
Ji *et al.*, 2021[15]	T2DM	IIIa	290/290	Once weekly Semaglutide, 1.0 mg	53.0±10.6	76.1±16.3	27.9±5.0	30	①⑥⑦⑧⑨⑩⑱⑲⑳㉓
				Once daily Sitagliptin, 100 mg	53.1±10.4	75.5±14.7	27.3±4.7		
Friedrichsen *et al.*, 2021[16]	No	I	36/36	Once weekly semaglutide, 2.4 mg	40.7±12.2	106.2±16.2	34.2±3.0	20	①⑰ ⑱ ⑲⑳㉒㉓
				Placebo	45.0±9.5	104.9±14.0	34.6±3.1		
Davies *et al.*, 2021[17]	T2DM	III	404/403	Once weekly semaglutide, 2.4 mg	55±11	99.9±22.5	35.9±6.4	68	①②③④⑥⑦⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉓
				Placebo	55±11	100.5±20.9	35.9±6.5		
Wadden *et al.*, 2021[18]	No	IIIa	407/204	Once weekly semaglutide, 2.4 mg	46±13	106.9±22.8	38.1±6.7	68	①②③④⑤⑥⑦⑧⑨⑪⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉒㉓
				Placebo	46±13	103.7±22.9	37.8±6.9		
Rubino *et al.*, 2022[19]	No	IIIb	126/127	Once weekly semaglutide, 2.4 mg	48±14	102.5±25.3	37.0±7.4	68	①②③④⑤⑦⑧⑨⑩⑪⑫⑬⑭⑮⑯⑰⑱⑲⑳㉑㉓
				Once daily liraglutide, 3.0 mg	49±13	103.7±22.5	37.2±6.4		
Kellerer *et al.*, 2022[20]	T2DM	IIIb	874/874	Once weekly semaglutide, 0.86 mg	60.8±9.4	87.6±18.1	31.4±5.5	52	②③⑰⑱⑲⑳
				Insulin	61.5±9.5	88.1±18.4	31.7±5.5		
Kadowaki *et al.*, 2022[21]	ALL	IIIa	199/101	Once weekly semaglutide, 2.4 mg	52±12	86.9±16.5	32.0±4.6	68	①②③④⑦⑰⑱⑲⑳㉑㉓
				Placebo	50±9	90.2±15.1	31.9±4.2		
Knop *et al.*, 2023[22]	No	III	334/333	Oral semaglutide, 50 mg/qd	49±13	104.5±22.0	37.3±6.3	68	①②③④⑤⑥⑦⑧⑨⑩⑪⑰⑱⑲⑳㉑㉓
				Placebo	50±12	106.2±22.3	37.7±6.8		
Frias *et al.*, 2023[23]	T2DM	II	31/30	Semaglutide, 2.4 mg	57±10	105.4±24.9	36.2±7.2	32	①③④⑩⑪⑰⑱⑲⑳㉑
				Cagrilintide	62±7	107.4±25.0	34.4±6.1		
Iijima *et al.*, 2023[24]	T2DM	NA	16/16	Once weekly semaglutide, 0.5 mg	61.5±11.2	72.3–20.2	27.0–6.6	26	①⑧⑨⑩⑪⑱⑲⑳㉑
				Once weekly dulaglutide, 0.75 mg	62.7±12.0	72.0–14.9	25.1–3.9		

①=Body weight (kg); ②=The proportion of patients with weight loss >5%; ③=The proportion of patients with weight loss >10%; ④=The proportion of patients with weight loss >15%; ⑤=The proportion of patients with weight loss >20%; ⑥=BMI; ⑦=Waist circumference; ⑧=SBP; ⑨=DBP; ⑩=HbA1c; ⑪=FPG; ⑫=TC; ⑬=TG; ⑭=HDL; ⑮=LDL; ⑯=VLDL; ⑰=Adverse events; ⑱=Nausea; ⑲=Diarrhea; ⑳=Vomiting; ㉑=Constipation; ㉒=Abdominal pain; ㉓=Nasopharyngitis; BMI=Body mass index; HbA1c=Glycosylated hemoglobin A1c; TC=Total cholesterol; TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; VLDL=Very LDL; DBP=Diastolic blood pressure; SBP=Systolic blood pressure, T2DM=Type 2 diabetes; NA=Not available; ALL=Acute lymphoblastic leukemia; FPG=Fasting plasma glucose

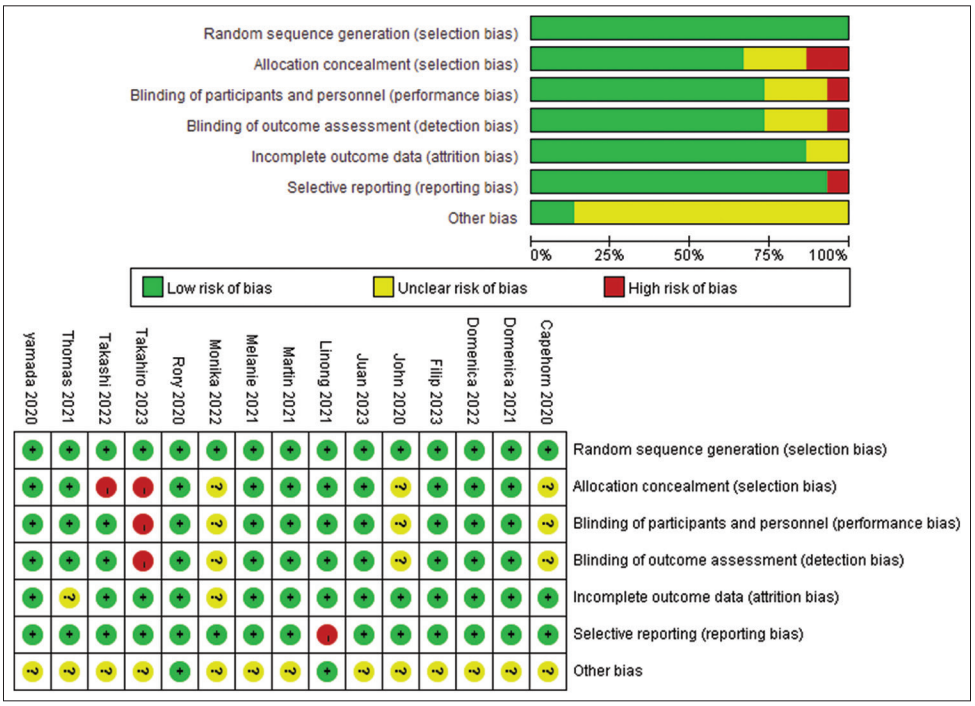

Figure 2: Methodological quality assessment of included studies

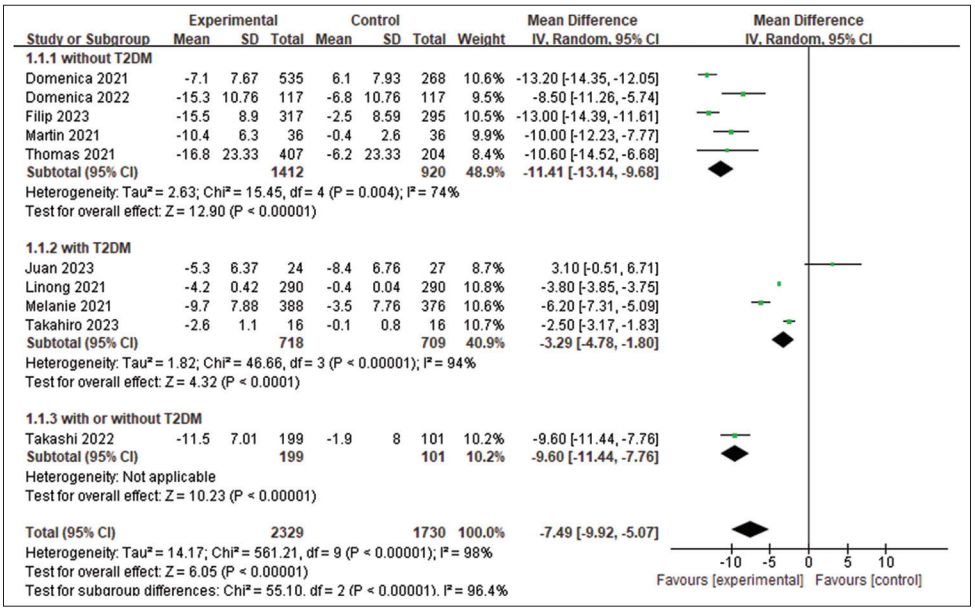

Figure 3: Forest plot of meta-analysis of the body weight loss in two groups

Waist circumference

Eight RCTs[12,14,15,17-19,21,22] reported the value of the reduction in patients' waist circumference. There was statistical heterogeneity among the studies ($P < 0.001$, $I^2 = 97\%$), so a random-effects model was chosen, and subgroup analysis was performed, and the results are shown in Figure 6. Compared with the control group, in the semaglutide group, more waist circumference reductions were reported in all of the included trials (MD = −7.26, 95% CI [−9.94, −4.58], $P < 0.001$). The subgroup results showed that in overweight or obese patients without diabetes (MD = −9.05, 95% CI [−10.42, −7.67], $P < 0.001$), overweight or obese patients with diabetes (MD = −4.01, 95% CI [−5.35, −2.66], $P < 0.001$), and overweight or obese patients with or without diabetes (MD = −9.30, 95% CI [−10.99, −7.61], $P < 0.001$), the waist circumference reductions in the semaglutide group were significantly more than those in the control group, and the difference was statistically significant.

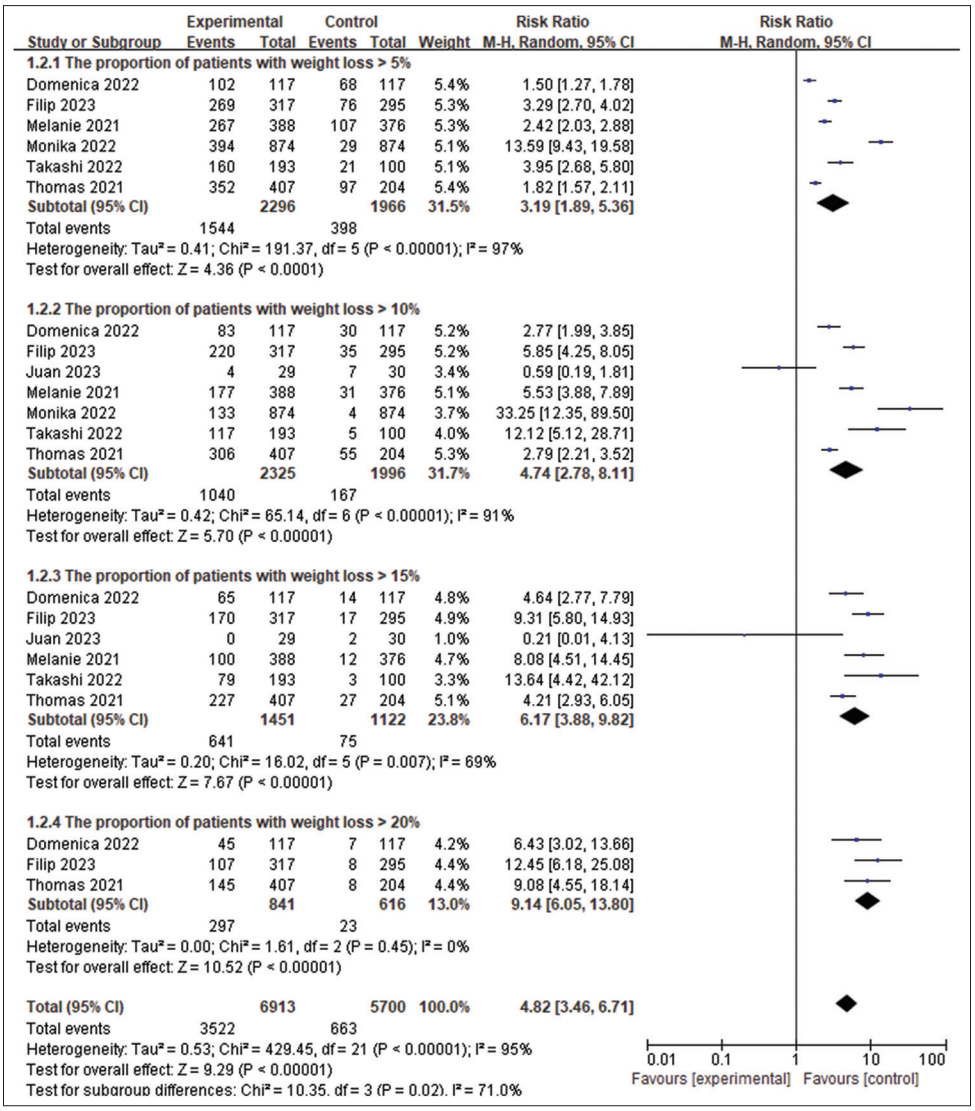

Figure 4: Forest plot of meta-analysis of proportion lost more than 5%, 10%, 15% and 20% in two groups

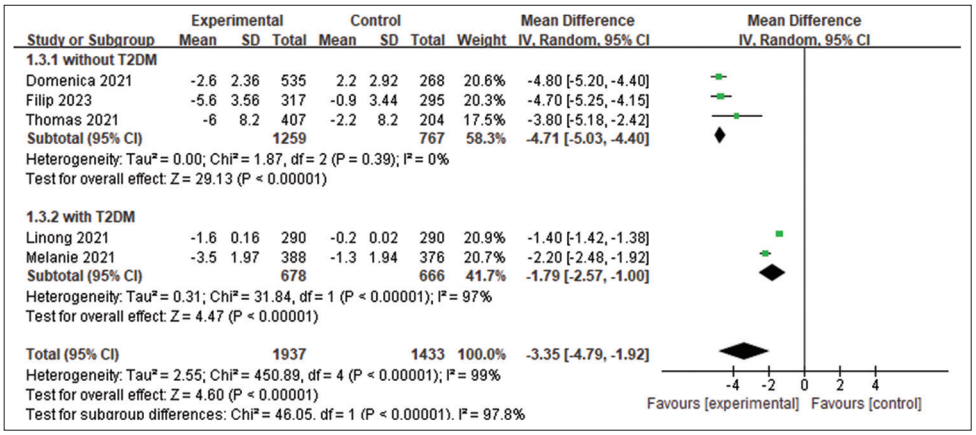

Figure 5: Forest plot of meta-analysis of body mass index decline in two groups

Other efficacy outcome indicators

Seven RCTs[14,15,17-19,22,24] reported the values of the patient's blood pressure changes, and the results are shown in Table 2. The SBP reductions in the semaglutide group (RR = −3.37, 95% CI [−5.32, −1.42], $P < 0.001$) were higher than those in the control group, with a statistically significant difference, and the DBP reductions (RR = −0.83, 95% CI [−1.79, 0.13], $P = 0.09$) was slightly closer to

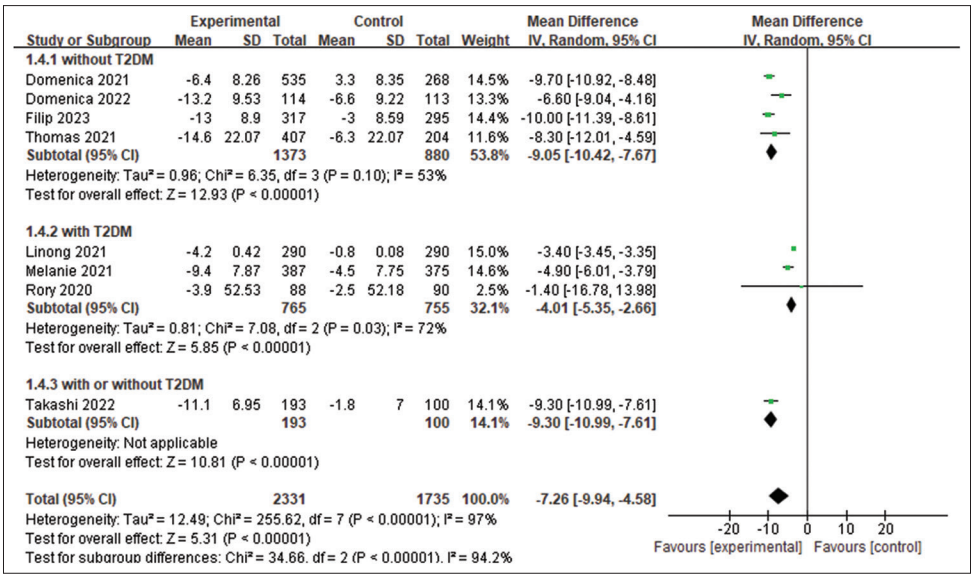

Figure 6: Forest plot of meta-analysis of waist circumference reduction in two groups

Table 2: Meta-analysis results of other outcome indicators in two groups

Outcome indicators	Study	Sample	I^2 (%)	Effect model	MD/RR (95% CI)	*P*
SBP	7	3627	87	Random effects model	−3.37 (−5.32−−1.42)	0.0007
DBP	7	3627	73	Random effects model	−0.83 (−1.79-0.13)	0.09
HbA1c	7	3038	99	Random effects model	−0.66 (−1.07−−0.25)	0.002
FPG	7	3076	93	Random effects model	−4.81 (−7.03−−2.60)	0.0001
TC	4	2390	94	Random effects model	−4.44 (−8.85−−0.04)	0.05
TG	4	2389	91	Random effects model	−11.07 (−22.15-0.01)	0.05
HDL	4	2380	0	Fixed effects model	−0.00 (−0.04-0.04)	0.99
LDL	4	2389	88	Random effects model	−4.80 (−10.10-0.50)	0.08
VLDL	4	2389	91	Random effects model	−11.02 (−22.08-0.04)	0.05
Nausea	14	6792	91	Random effects model	3.21 (2.05-5.01)	0.00001
Diarrhea	14	6792	13	Fixed effects model	1.86 (1.63-2.11)	0.00001
Vomiting	13	6695	78	Random effects model	3.76 (2.29-6.18)	0.00001
Constipation	11	4402	56	Random effects model	1.90 (1.45-2.49)	0.0001
Abdominal pain	4	2062	0	Fixed effects model	2.62 (1.72-4.01)	0.00001
Nasopharyngitis	10	4385	0	Fixed effects model	0.93 (0.81-1.08)	0.37

HbA1c=Glycosylated hemoglobin A1c; TC=Total cholesterol; TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; VLDL=Very LDL; DBP=Diastolic blood pressure; SBP=Systolic blood pressure, MD=Mean difference; RR=Relative risk; CI=Confidence interval; FPG=Fasting plasma glucose

the control group, and the difference was not statistically significant. In addition, the values of glycated hemoglobin reduction (RR = −0.66, 95% CI [−1.07, −0.25], P = 0.002) and fasting glucose reduction (RR = −4.81, 95% CI [−7.03, −2.60], P < 0.001) were higher than those of the control group, which were statistically different. Four RCTs[14,17-19] were included to analyze the effects on lipid metabolism, and the values of TG reduction (RR = −4.44, 95% CI [−8.85, −0.04], P = 0.05), TC reduction (RR = −11.07, 95% CI [−22.15, 0.01], P = 0.05), LDL reduction (RR = −4.80, 95% CI [−10.10, 0.50], P = 0.08), and VLDL reductions (RR = −11.02, 95% CI [−22.08, 0.04], P = 0.05) were slightly higher than those of the control group, but the differences were not statistically significant; HDL reductions (RR = −0.00, 95% CI [−0.04, 0.04], P = 0.99) were not statistically significantly different from the control group. For the sensitivity analysis of the results of the meta-analysis of TC, TG, LDL, and VLDL, after the exclusion of the included study of Davies *et al*.,[17] there was a significant change in the MD value and 95% CI. The reduction values of all categories were higher than those of the control group, and the difference was statistically significant.

Adverse drug reaction

Fourteen RCTs[10,11,13-24] reported ADR, among which 11 RCTs counted the incidence of total ADR. The results are shown in Figure 7. The incidence of total ADR in the semaglutide group (RR = 1.04, 95% CI [0.99, 1.04], P = 0.1) was slightly higher than that in the control group, but the difference was not statistically significant. The incidence of nausea, vomiting, diarrhea, abdominal pain, and constipation was significantly higher in the semaglutide group than in the control group,

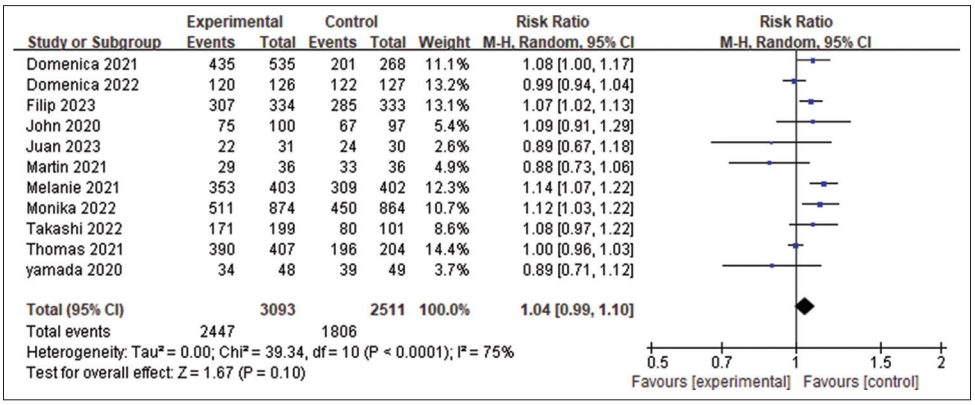

Figure 7: Forest plot of meta-analysis of total adverse events in two groups

and the difference was statistically significant. The incidence of nasopharyngitis was higher in the semaglutide group than in the control group, but the difference was not statistically significant, as shown in Table 2.

Sensitivity analysis

The results of the sensitivity analysis using weight as an indicator showed that after excluding the included studies one by one, the reduction in heterogeneity before and after the exclusion was not statistically significant, suggesting that the results of this study are relatively robust. The results obtained for the remaining indicators (percentage of weight loss >5%, 10%, 15%, and 20%, BMI, and waist circumference) were more stable. In terms of blood pressure, the exclusion of the study by Iijima *et al*.[24] showed a statistically significant reduction in DBP in the semaglutide group, which may have been terminated early in the preliminary analysis and with a duration of only 26 weeks and a sample size of only 32, which may have affected the robustness of the results. In terms of lipid metabolism, excluding the study of Davies *et al*.,[17] the semaglutide group was able to significantly reduce TC, TG, LDL, and VLDL, with a statistically significant difference.

Publication bias

Using body weight as an indicator, an inverted funnel plot was drawn, and the results are shown below, suggesting a low likelihood of publication bias in this study [Figure 8].

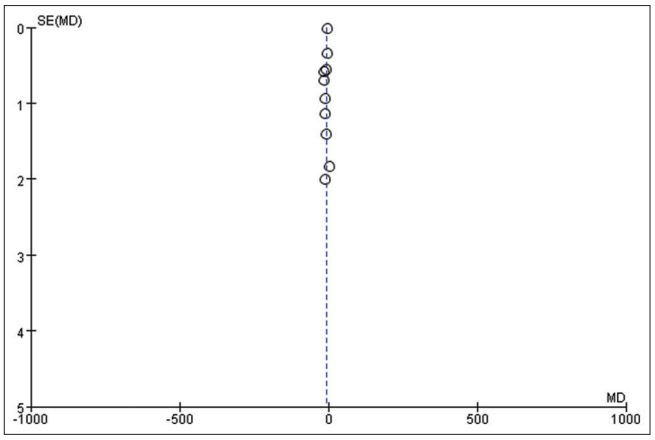

Figure 8: Funnel plot for the publication bias analysis of body weight

DISCUSSION

The purpose of this article was to examine, in a pooled fashion, the efficacy and safety of semeglutide compared with placebo or other hypoglycemic agents in obese or overweight adult patients with or without diabetes mellitus. The results revealed that semaglutide was more effective than placebo or other hypoglycemic drugs in reducing body weight, BMI, and waist circumference in overweight or obese patients. In addition, semaglutide showed promising results in improving blood pressure and blood glucose, as well as other lipid metabolism. No serious adverse effects were reported during the study.

The weight-reducing utility of GLP-1 receptor agonists has attracted widespread attention since scientists first discovered that GLP-1 receptor agonists could reduce body weight in diabetic patients at the beginning of the 21st century. Since then, several GLP-1 receptor agonists have been shown to reduce body weight.[25,26] Liraglutide and semaglutide were approved by the FDA for overweight or obese indications and were launched in 2014 and 2021, respectively. Up to this point, there have been several articles analyzing the weight reduction effects of semaglutide, but some of them only unilaterally focused on the impact on diabetic or nondiabetic patients,[27-31] and Xiaodong *et al*.[32] only included semaglutide 2.4 mg versus placebo-controlled studies. However, they used overweight or obese patients with or without diabetes as their study subjects. In this paper, we have made relevant expansions and updates based on the previous authors, not limited to the control with placebo and the dose and dosage form of semaglutide. We also selected the studies with other glucose-lowering drugs (such as liraglutide, sitagliptin, canagliflozin, dulaglutide, insulin, and cagrilintide) in comparison with each other. By screening and evaluating the latest

studies in the past 3 years, a total of 15 RCTs comparing semaglutide with placebo or other glucose-lowering drugs in weight reduction, totaling 6984 patients, were included to systematically evaluate the efficacy and safety of semaglutide in weight reduction. The results showed that when semaglutide was given orally or intravenously, it was more effective than the control group (placebo or other hypoglycemic agents) in reducing body weight, the proportion of patients with weight loss >5%, 10%, 15%, and 20%, BMI, and waist circumference; In terms of the effect on glycated hemoglobin and FBG, the semaglutide group was able to reduce both values compared with the control group effectively, and the difference was statistically significant, which is a good choice for overweight or obese patients with type 2 diabetes mellitus. These results are similar to those of Yaqiong *et al*. and Xiaodong *et al*.[29,32] In addition, this paper also analyzes the effect of semaglutide on blood pressure and lipid metabolism, and the reduction of SBP and TC was statistically significant compared with the control group. The differences were not statistically significant for DBP, TG, HDL, LDL, and VLDL. Still, the reductions were slightly higher than those in the control group, suggesting potential cardiovascular benefits. It has been proved that semaglutide can reduce cardiovascular risk associated with overweight and obesity in the absence of diabetes.[33]

Enteroglucagon mainly refers to glucose-dependent insulinotropic polypeptide and GLP-1, the latter of which is produced by intestinal L-cells after energy intake. GLP-1 binds to its specific receptors and not only promotes pancreatic cells to synthesize and release insulin but also directly inhibits the secretion of pancreatic islet α-cells of glucagon, optimizing adipose tissue oxidation and hindering hepatic gluconeogenesis.[34,35] Semaglutide belongs to long-acting GLP-1 receptor agonists with specific structural modifications that bind tightly to albumin and reduce the degradation of dipeptidyl peptidase 4 while also allowing a high enough GLP-1R affinity to lessen renal clearance so that its preparations degrade slowly, with a half-life of up to 155–184 h, and are capable of exerting a long-lasting effect.[36] However, the mechanism of its weight-loss effect is still not very clear. Several studies have found that it may be related to the binding of simethicone to the GLP-1 receptor in the brain to mediate weight loss. Some studies[37] have proposed that semaglutide may modulate the areas of the human brain involved in regulating eating behavior through primary and secondary activation, thereby reducing the body's craving for food and decreasing the feeling of hunger. In this regard, Gabery *et al*.[38] also illustrated that semaglutide directly enters the brainstem, septal nuclei, and hypothalamus and interacts with the brain through several specific sites in the periventricular organs and neighboring ventricles, inducing central c-Fos activation in 10 brain regions, activation that may involve termination of feeding controlled by neurons of the lateral parabrachial nucleus. Although GLP-1RA treatment has been shown to delay gastric emptying up to 1 h after a meal, overall gastric emptying does not appear to be affected. It has been found that GLP-1RA is associated with a reduction in appetite and hunger, a decreased preference for high-energy foods, an altered food reward pathway, a reduction in food cravings, and an improvement in dietary control, which provides evidence for the role of GLP-1RA treatment in inducing weight loss giving evidence for a mechanism of action.[39] As for safety, the adverse effects of semaglutide are mainly gastrointestinal, such as nausea, vomiting, abdominal pain, and diarrhea, which is consistent with previous studies. Wharton *et al*.[40] suggest that the weight-loss effects of semaglutide are largely irrelevant. Even though semaglutide has been confirmed to be effective in weight loss, some studies have shown weight rebound in subjects after discontinuing the drug.[41] Hence, ongoing treatment combined with lifestyle intervention is required to maintain improvements in weight.

There are many limitations of this article: first, a total of 15 papers were included in the article, but some of them had small sample sizes, which may affect the robustness of the results due to insufficient sample sizes; second, due to the differences in drug types, dosages, regimens, and gender ratios in the included papers, no further stratified analyses were performed; and then, there were fewer studies comparing with other hypoglycemic drugs.

CONCLUSION

In summary, this study mainly analyzed the effects of semaglutide versus placebo or glucose-lowering drugs such as liraglutide, dulaglutide, and cagliflozin, on body weight, which demonstrated a better quality of weight loss in obese or overweight patients with or without diabetes, and better potential benefits in terms of glucose, blood pressure, and lipids but with an increase in gastrointestinal adverse effects. Larger sample sizes and higher-quality clinical data are needed further to investigate the role of semaglutide in weight loss.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1: The search strategy of cochrane library, embase and pubMed

Database	Search strategy
Cochrane Library	#1 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees #2 (semaglutide):ti, ab, kw OR (wegovy):ti, ab, kw OR (ozempic):ti, ab, kw OR (nn9934):ti, ab, kw OR (nn9935):ti, ab, kw OR (nn9936):ti, ab, kw OR (glp-1 ra):ti, ab, kw OR (glucagon-like peptide 1):ti, ab, kw OR (glucagon-like peptide 1 receptor agonist):ti, ab, kw OR (GLP-1):ti, ab, kw #3 MeSH descriptor: [Randomized Controlled Trial] explode all trees #4 (randomized):ti, ab, kw OR (clinical trials):ti, ab, kw OR (rct):ti, ab, kw OR (randomly):ti, ab, kw OR (placebo):ti, ab, kw #5 MeSH descriptor: [Obesity] explode all trees #6 (obese):ti, ab, kw OR (overweight):ti, ab, kw OR (over weight):ti, ab, kw OR (weight gain):ti, ab, kw OR (adiposity):ti, ab, kw
Embase	#1 "obesity"/exp #2 "obesity"/exp OR obesity OR obese: ab, ti OR overweight: ab, ti OR "overweight":ab, ti OR "weight gain":ab, ti OR adiposity: ab, ti #3 "semaglutide"/exp #4 "wegovy"/exp OR wegovy OR ozempic: ab, ti OR nn9934:ab, ti OR nn9935:ab, ti OR nn9936:ab, ti OR "glp-1 receptor agonist":ab, ti OR "glp-1 ra":ab, ti OR "glucagon-like peptide 1":ab, ti OR "glucagon-like peptide 1 receptor agonist":ab, ti #5 "randomized controlled trial"/exp #6 randomized OR "clinical trials":ab, ti OR rct: ab, ti OR randomly: ab, ti OR placebo: ab, ti
PubMed	1. obesity [Mesh] OR obese [Title/Abstract] OR overweight [Title/Abstract] OR over weight [Title/Abstract] OR weight gain [Title/Abstract] OR adiposity [Title/Abstract] OR rybelsus [Title/Abstract] 2. semaglutide [Title/Abstract] OR wegovy [Title/Abstract] OR ozempic [Title/Abstract] OR NN9934 [Title/Abstract] OR NN9935 [Title/Abstract] OR NN9936 [Title/Abstract] OR GLP-1 receptor agonist [Title/Abstract] OR GLP-1 RA [Title/Abstract] OR glucagon-like peptide 1 [Title/Abstract] OR glucagon-like peptide 1 receptor agonist [Title/Abstract] 3. randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR Clinical Trials [Title/Abstract] OR RCT [Title/Abstract] OR randomly [Title/Abstract] OR placebo [Title/Abstract]/ 4. ((((((((((obesity[MeSH Terms]) OR (obesity[Title/Abstract])) OR (obese[Title/Abstract])) OR (overweight[Title/Abstract])) OR (over weight[Title/Abstract])) OR (weight gain[Title/Abstract])) OR (adiposity[Title/Abstract])) OR (rybelsus[Title/Abstract])) AND ((((((((((semaglutide[MeSH Terms]) OR (wegovy[Title/Abstract])) OR (ozempic[Title/Abstract])) OR (NN9934[Title/Abstract])) OR (NN9935[Title/Abstract])) OR (NN9936[Title/Abstract])) OR (GLP-1 receptor agonist[Title/Abstract])) OR (GLP-1 RA[Title/Abstract])) OR (glucagon-like peptide 1[Title/Abstract])) OR (glucagon-like peptide 1 receptor agonist[Title/Abstract]))) AND ((((((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract])) OR (Clinical Trials[Title/Abstract])) OR (RCT[Title/Abstract])) OR (randomly[Title/Abstract])) OR (placebo[Title/Abstract]))