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Efficacy and Safety of the New Appetite Suppressant, Liraglutide: A Meta-Analysis of Randomized Controlled Trials

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Background: Obesity is a chronic disease associated with metabolic diseases such as diabetes and cardiovascular disease. Since the U.S. Food and Drug Administration approved liraglutide as an anti-obesity drug for nondiabetic patients in 2014, it has been widely used for weight control in overweight and obese people. This study aimed to systematically analyze the effects of liraglutide on body weight and other cardiometabolic parameters.

Methods: We investigated articles from PubMed, EMBASE, and the Cochrane Library to search randomized clinical trials that examined body weight changes with liraglutide treatment.

Results: We included 31 studies with 8,060 participants for this meta-analysis. The mean difference (MD) between the liraglutide group and the placebo group was −4.19 kg (95% confidence interval [CI], −4.84 to −3.55), with a −4.16% change from the baseline (95% CI, −4.90 to −3.43). Liraglutide treatment correlated with a significantly reduced body mass index (MD: −1.55; 95% CI, −1.76 to −1.34) and waist circumference (MD: −3.11 cm; 95% CI, −3.59 to −2.62) and significantly decreased blood pressure (systolic blood pressure, MD: −2.85 mm Hg; 95% CI, −3.36 to −2.35; diastolic blood pressure, MD: −0.66 mm Hg; 95% CI, −1.02 to −0.30), glycated hemoglobin (MD: −0.40%; 95% CI, −0.49 to −0.31), and low-density lipoprotein cholesterol (MD: –2.91 mg/dL; 95% CI, −5.28 to −0.53; MD: −0.87% change from baseline; 95% CI, −1.17 to −0.56).

Conclusion: Liraglutide is effective for weight control and can be a promising drug for cardiovascular protection in overweight and obese people.

Keywords: Liraglutide; Glucagon-like peptide 1; Obesity; Metabolic syndrome; Meta-analysis

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INTRODUCTION

Obesity is a chronic disease associated with metabolic diseases such as diabetes, cardiovascular disease, chronic kidney disease, and cancer [1]. The rising prevalence of obesity has led to its recognition as a serious public health problem worldwide [2]. Lifestyle modification is the first step in controlling body weight in overweight and obese individuals [3]. Although lifestyle modification is the most effective strategy to manage body weight and prevent the metabolic complications of obesity, compliance with a healthy lifestyle proves difficult for many individuals. Dalle Grave et al. [4] reported that, despite the efficacy of lifestyle modification for reducing body weight, 70% to 80% of patients treated with lifestyle modification failed to maintain a reduced body weight at 3 to 5 years.

Pharmacotherapy is the next best option for weight control. The U.S. Food and Drug Administration (FDA) has approved four agents (orlistat, naltrexone-bupropion, phentermine-topiramate, and liraglutide) for long-term weight control, and of these, phentermine-topiramate and liraglutide are the most effective agents for weight control [5]. Liraglutide is a long-acting analog, with 87% homology to human glucagon-like peptide 1 (GLP-1), that acts as a GLP-1 receptor agonist [6].This drug was originally used only for glycemic control for people with diabetes. However, after several clinical trials reported a weight-reduction effect without hypoglycemia in obese people without diabetes [7], the FDA approved liraglutide for the treatment of obesity in 2014.

Many human and animal studies have shown the beneficial effects of GLP-1 receptor agonists in the brain and in peripheral tissues, besides their glucose-lowering effects [7,8]. GLP-1 receptor agonists increase insulin secretion from pancreatic beta cells, reduce insulin resistance and gluconeogenesis in the liver, slow gastric emptying, and reduce appetite [7]. This study aimed to investigate the effects of liraglutide on body weight and cardiovascular benefits. Therefore, we performed a meta-analysis of randomized controlled trials (RCTs) to assess liraglutide treatment in overweight and obese individuals.

METHODS

Search strategy

The literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table S1) [9], and the data were extracted by two researchers (S.M. and C.M.O.). S.M. extracted data from citation databases, including PubMed, EMBASE, and the Cochrane Library, from the inception of the database to March 7, 2021, and C.M.O. crosschecked these data for accuracy. Search terms included combinations of "liraglutide" and "obesity."

Study selection

The inclusion criteria were as follows: (1) population: participants who were overweight or obese (body mass index [BMI] $\geq$25 kg/m^2); (2) intervention: 1.8 or 3.0 mg liraglutide injection daily for 4 weeks or more; (3) comparators: control group with placebo; (4) outcomes: data on changes in the following variables: weight, waist circumference (WC), BMI, blood pressure, glycated hemoglobin (HbA1c), or low-density lipoprotein cholesterol (LDL-C); and (5) study design: RCTs.

The exclusion criteria were as follows: (1) articles on animal studies or in vivo experiments, only abstracts, and non-original articles, including expert opinions or reviews; (2) non-RCT studies; (3) studies on non-obese patients; and (4) studies involving participants with diseases that could affect weight change.

Data extraction

The following variables were extracted from the articles selected by two researchers (S.M. and C.M.O.) using the same criteria: first author, publication year, characteristics of the participants, number of study participants, mean age, weight, WC, BMI, blood pressure, HbA1c, and LDL-C.

Quality assessment

Two researchers (S.M. and C.M.O.) evaluated the quality of RCTs using the "Revised Cochrane risk-of-bias tool for randomized trials (ROB-2.0)." Discrepancies were resolved through discussions with a third investigator (S.H.Y.).

Data analyses and statistical methods

The pooled effect sizes were presented as mean differences (MD) and 95% confidence intervals (CIs) between the intervention group and the placebo group using the random effects model. Because the weight and LDL-C levels were reported by two different parameters, such as mean change or percentage change from baseline, we calculated the standard mean differences (SMD) of these variables. The heterogeneity between studies was tested using Cochrane Q statistic and Higgins I^2 statistic; an I^2 greater than 50% was considered indicative of heterogeneity between studies. Publication bias was evaluated using the funnel

plot and Egger's test, and sensitivity analyses were conducted between studies. In addition, subgroup analysis was performed based on the dosage of liraglutide and the presence of diabetes. All analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat, Englewood, NJ, USA).

RESULTS

Study characteristics

A total of 2,591 articles (PubMed 844, EMBASE 1,153, Cochrane Library 594) were identified on the literature search; 676 overlapping articles were excluded, and 1,915 articles were verified for further screening. After excluding articles that did not meet the inclusion criteria, 101 studies were assessed for eligibility. After further review and quality assessment, 31 studies were included in the meta-analysis (Fig. 1) [10-39], and a total of 8,060 participants were included. There were three and 28 studies in obese adolescents and adults, respectively. Nine of the studies in adults only included obese or overweight patients with diabetes, and 12 studies included obese or overweight patients without diabetes. The main baseline characteristics of each study are summarized in Table 1 [10-40]. In the quality assessment, the risk-of-bias was low in 27 studies [10-15,17-22, 24-28,30-37,39]. Four RCTs had some concerns with regard to bias arising because of deviations from the intended interventions [16,23,29,38].

Effect of liraglutide on changes in anthropometric data

Twenty-four studies [10-14,16-22,24,25,27,28,30-34,37-39] with 7,742 participants (liraglutide group 4,721; placebo group 3,021) reported changes in weight from the baseline. The SMD between the liraglutide group and the placebo group on using a random effects model was –0.71 (95% CI, −0.81 to −0.61), which indicated significantly more weight loss in the liraglutide group, and the I^2 was 65.6%, indicating significant heterogeneity (Fig. 2). The funnel plot was symmetrical, and publication bias was not detected (Egger's test: P=0.97) (Supplemental Fig. S1). In sensitivity analysis, the significance of the results did not change even after each study was removed, and no outliers were observed (Supplemental Fig. S2).

Twenty one studies [12-14,16-22,24,25,28,30-34,37-39] with 6,228 participants (liraglutide group 3,756; placebo group 2,472) reported changes in weight (kg) from the baseline (MD, −4.19 kg; 95% CI, −4.84 to −3.55). Thirteen studies [10-13,16,18,19,25,27,28,32-34] with 6,699 participants (liraglutide group 4,146; placebo group 2,553) reported percentage changes

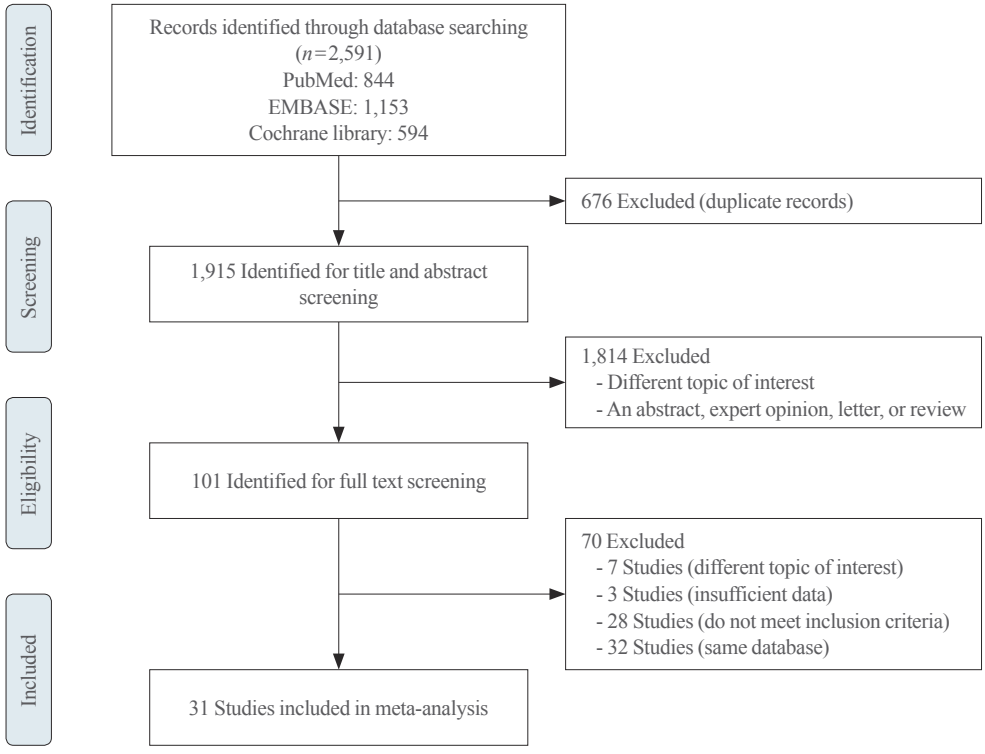

Fig. 1. Schema of the search strategy.

Table 1. Baseline Characteristics of the Participants in 23 Randomized Control Trials Included in the Present Meta-Analysis

Study	Study duration and dosage of liraglutide	No. of intervention	No. of control	Diabetes mellitus	Age, yr	Weight, kg	Waist circumference, cm	BMI, kg/m^2	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg	HbA1c, %	LDL-C, mg/dL
Ahmadi et al. (2019) [17]	24 wk 1.8 mg/day	63	59	122 (100)	I: 63.8±8.2 C: 63.6±7.7	I: 98.8±14.1 C: 99.8±14.8	I: 116.1±10.2 C: 115.7±10.6	I: 33.7±4.3 C: 33.5±4.0	I: 138 (17) C: 134 (14)	I: 74±13 C: 75±9	I: 8.98±0.99 C: 8.96±1.10	I: 86±31 C: 88±37
Armstrong et al. (2016) [33]	48 wk 1.8 mg/day	26	26	17 (33)	I: 50±11 C: 52±12	I: 101±18 C: 108±18	I: 110±11 C: 108±18	I: 34.2±4.7 C: 37.7±6.2	I: 130±13 C: 133±12	I: 79± 11 C: 78± 9	I: 5.9±0.7 C: 6.0±0.9	I: 100±31 C: 112±39
Astrup et al. (2009) [31]	20 wk 1.2–3 mg/day	3:93 1.8:90	98	0	I 3: 45.9±10.7 1.8: 45.5±10.9 C: 45.9±10.3	I 3: 97.6±13.7 1.8: 98.0±12.5 C: 97.3±12.3	NR	I 3: 34.8±2.8 1.8: 35.0±2.6 C: 34.9±2.8	I 3: 124±11.3 1.8: 123±13 C: 124±11.1	I 3: 77.8±8.3 1.8: 77.9±7.9 C: 76.8±8.5	NR	I 3: 131±30 1.8: 137±34 C: 137±34
Bensignor et al. (2021) [36]	52 wk 0.6 mg–1.8 mg/day	66	68	134 (100)	I: 14.6±1.7 C: 14.6±1.7	NR	I: 106.1±20.7 C: 104.3±15.0	I: 34.6±10.9 C: 33.3±7.4	NR	NR	NR	NR
Blackman et al. (2016) [25]	32 wk 3 mg/day	180	179	0	I: 48.6±9.9 C: 48.4±9.5	I: 116.5±23 C: 119±25	I: 122.3±14.5 C: 122.7±14.9	I: 38.9±6.4 C: 39.4±7.4	I: 126±12 C: 127±12	I: 81±8 C: 82±9	I: 5.7±0.4 C: 5.6±0.4	I: 112±29 C: 111±27
Danne et al. (2017) [24]	5 wk 3 mg/day	14	7	0	I: 15.1±0.9 C: 14.4±1.8	I: 103.5±12.8 C: 109.6±30.8	NR	I: 36.5±3.7 C: 35.7±5.4	I: 124±14 C: 126±7	I: 61±9 C: 60±6	I: 5.4±0.3 C: 5.5±0.3	NR
Davies et al. (2015) [27]	56 wk 1.8 and 3 mg/day	3:423 1.8:211	212	846 (100)	I 3: 55.0±10.8 1.8: 54.9±10.7 C: 54.7±9.8	I 3: 105.7±21.9 1.8: 105.8±21.0 C: 106.5±21.3	I 3: 118.0±14.4 1.8: 117.5±14.7 C: 117.3±14	I 3: 37.1±6.5 1.8: 37.0±6.9 C: 37.4±7.1	I 3: 129±14 1.8: 131±15 C: 129±14	I 3: 79±8.6 1.8: 80±9 C: 79.3±10	I 3: 7.9±0.8 1.8: 8.0±0.8 C: 7.9±0.8	I 3: 86.4±36 1.8: 92±38.5 C: 85.2±39
de Wit et al. (2016) [29]	26 wk 1.8 mg/day	25	22	47 (100)	NR	NR	I: 110±13 C: 107±15	I: 33.6±6.4 C: 31.6±5.1	I: 137±16 C: 141±15	I: 81±6 C: 82±8	NR	NR
Frossing et al. (2018) [20]	26 wk 1.8 mg/day	48	24	0	NR	I: 94.2±15.4 C: 91.3±13.6	I: 102.6±10.8 C: 102.6±11.1	I: 33.3±5.1 C: 33.3±4.6	I: 123±9 C: 124±9	I: 79±8 C: 80±7	I: 5.3 C: 5.3	I: 109±27 C: 116±21
Garvey et al. (2020) [10]	56 wk 3 mg/day	198	198	396 (100)	I: 55.9±11.3 C: 57.6±10.4	I: 100.6±20.8 C: 98.9±19.9	I: 114.8±13.7 C: 114.2±13.2	I: 35.9±6.5 C: 35.3±5.8	I: 129±14 C: 132±16	I: 78±9 C: 78±9	I: 7.9±1.1 C: 8.0±1.0	I: 94±33 C: 94±29
Gudbergsen et al. (2021) [37]	52 wk 3 mg/day	80	76	NR	I: 59.2±10.8 C: 59.3±9.7	I: 96.3±18.2 C: 90±14.3	I: 105.5±13.9 C: 101.8±11.1	I: 32.8±5.5 C: 31.3±4.0	NR	NR	NR	NR
Guo et al. (2020) [38]	26 wk 1.8 mg/day	31	30	61 (100)	I: 53.1±6.3 C: 52.6±3.9	I: 84.3±10.8 C: 82.2±12.4	I: 95.5±8.0 C: 82.2±12.4	I: 29.2±4.2 C: 28.6 ±3.7	NR	NR	I: 7.5±1.3 C: 7.3±1.6	I: 127±23 C: 115±19
Kelly et al. (2020) [12]	56 wk 3 mg/day	125	126	NR	I: 14.6±1.6 C: 14.5±1.6	I: 99.3±19.7 C: 102.2±21.6	I: 104.9±12.7 C: 107±13.6	I: 35.3±5.1 C: 35.8±5.7	I: 116±10 C: 117±12	I: 72±8 C: 73±8	I: 5.3±0.4 C: 5.3±0.4	I: 88.6±24 C: 86.6±25
Khoo et al. (2019) [16]	26 wk 3 mg/day	15	15	NR	I: 38.6±8.2 C: 43.6±9.9	I: 102.7±16.2 C: 89.6±12.7	I: 111.1±10.7 C: 105.8±7.6	I: 34.3±3.9 C: 32.2±3.2	NR	NR	NR	NR
Kim et al. (2013) [30]	14 wk 1.8 mg/day	24	27	0	I: 45.2±12.1 C: 45.0±12	NR	NR	I: 31.9±2.7 C: 31.9±3.5	NR	NR	NR	NR
Kumarathurai et al. (2017) [22]	12 wk 1.8 mg/day	27	27	27 (100)	61.8±7.6	96.9±17.1	31.6±4.8	31.6±4.8	139.3±19.4	80.2±10.1	6.4±0.5	89±27

(*Continued to the next page*)

Table 1. Continued

Study	Study duration and dosage of liraglutide	No. of intervention	No. of control	Diabetes mellitus	Age, yr	Weight, kg	Waist circumference, cm	BMI, kg/m^2	Systolic blood pressure, mm Hg	Diastolic blood pressure, mm Hg	HbA1c, %	LDL-C, mg/dL
Iacobellis et al. (2017) [23]	24 wk 1.8 mg/day	49	36	85 (100)	I: 50±10 C: 52±10	I: 104.5±22.3 C: 87.3±18.3	NR	I: 37.8±7.3 C: 32.6±6.7	I: 128±17 C: 122±13	I: 79.5±8 C: 77.5±9	I: 6.6±0.8 C: 6.4±0.6	I: 100±43 C: 98±31
Larsen et al. (2017) [21]	66 wk 1.8 mg/day	47	50	NR	I: 42.1±10.7 C: 43.0±10.5	I: 103.3±16.1 C: 102.4±23.9	I: 117.3±12.4 C: 115.9±15.1	I: 33.7±5.1 C: 33.9±6.6	I: 126±11 C: 125±14.	I: 84±9.8 C: 84±7.6	I: 5.6±0.4 C: 5.5±0.4	I: 124± 58 C: 127±43
Lind et al. (2015) [26]	24 wk 1.8 mg/day	63	59	122 (100)	I: 63.8±8.2 C: 63.6±7.7	I: 98.8±14.1 C: 99.8±14.8	I: 116.1±10.2 C: 115.7±10.6	I: 33.7±4.3 C: 33.5±4.0	I: 138±17 C: 134±14	I: 74±13 C: 75±9	I: 8.98±0.99 C: 8.96±1.10	I: 86±31 C: 88±37
Nexoe-Larsen et al. (2018) [19]	12 wk 3 mg/day	26	26	0	I: 47.6±10.4 C: 47.5±9.7	I: 98.2±17.0 C: 99.8±14.7	NR	I: 32.5±3.6 C: 32.6±3.3	NR	NR	NR	NR
O'Neil et al. (2018) [18]	52 wk 3 mg/day	103	136	0	I: 49±11 C: 46±13	I: 108.7±21.9 C: 114.2±25.4	I: 116.2±13.8 C: 119.5±15.9	I: 38.6±6.6 C: 40.1±7.2	NR	NR	I: 5.5±0.4 C: 5.5±0.4	I: 120 C: 120
Peradze et al. (2019) [15]	5 wk 3 mg/day	20	20	3 (15)	NR	NR	NR	I: 35.5±5.8 C: 35.1±5.6	NR	NR	NR	I: 52±52 C: 52±52
Pi-Sunyer et al. (2015) [28]	56 wk 3 mg/day	2,437	1,225	0	I: 58±7 C: 58±8	I: 106.2±21.2 C: 106.2±21.7	I: 115.0±14.4 C: 114.5±14.3	I: 38.3±6.4 C: 38.3±6.3	I: 123±12.9 C: 123.2± 12.8	I: 78.7±8.6 C: 78.9±8.5	I: 5.6±0.4 C: 5.6±0.4	I: 111.6±27.9 C: 112.2± 27.6
Tronieri et al. (2020) [40]	52 wk 3 mg/day	37	36	NR	I: 44.3±11.7 C: 47.4±11.8	NR	NR	I: 39.2±5.0 C: 37.6±4.1	NR	NR	NR	NR
van Eyk et al. (2019) [14]	26 wk 1.8 mg/day	22	25	47 (100)	I: 59.9±6.2 C: 59.2±6.8	I: 98.4±13.8 C: 94.5±3.1	NR	I: 32.6±4.4 C: 31.6±3.4	I: C:	I: C:	I: 8.3±1.1 C: 8.1±0.9	I: 101±33 C: 99±35
Vedtofte et al. (2020) [39]	52 wk 1.8 mg/day	37	45	0	I: 38.8 (34.3–40.7) C: 38.3 (35.5–41.2)	I: 89.0 (87.4–107.2) C: 83.9 (76.3–92.6)0	I: 104 (99–110) C: 104 (101–106)	I: 32.1 (27.4–36.3) C: 30.6 (28.4–33.0)	I: 125 (121–129) C: 128 (125–132)	I: 80 (78–83) C: 82 (79–84)	I: 5.1 (5.0–5.3) C: 5.1 (5.0–5.2)	I: 127 (93–143) C: 112 (93–135)
Wadden et al. (2013) [32]	56 wk 3 mg/day	207	206	0	NR	I: 106.7±22.0 C: 105.0±22.5	I: 114.4±15.7 C: 112.7±15.2	I: 38.2±6.2 C: 37.5±6.2	I: 122.7±13.1 C: 123.2± 12.3	I: 78.0±8.4 C: 79.2±7.5	I: 5.6±0.4 C: 5.5±0.4	I: 112±27 C: 116±31
Wadden et al. (2019) [13]	52 wk 3 mg/day	50	50	0	I: 45.2±12.3 C: 49.5±11.0	I: 107.8±17.9 C: 105.8±14.7	I: 116.7±10.4 C: 116.7±11.6	I: 38.5±5.4 C: 38.0±4.3	I: 135±12 C: 139±14	I: 74±7 C: 78±10	I: 5.7±0.3 C: 5.6±0.3	I: 112±30 C: 117±30
Wadden et al. (2020) [11]	56 wk 3 mg/day	142	140	0	I: 45.4±11.6 C: 49±11.2	I: 108.5±22.1 C: 106.7±22	I: 116±14.4 C: 115±15.6	I: 39.3±6.8 C: 38.7±7.2	I: 125±15 C: 127±14	I: 80±9 C: 81±8	I: 5.5±0.4 C: 5.5±0.4	I: 112±31 C: 120±35
Wang et al. (2020) [35]	16 wk 3 mg/day	14	16	0	I: 36.4±8.9 C: 35.7±11.0	NR	NR	I: 37.0±4.3 C: 38.4±5.7	NR	NR	NR	NR
Whicher et al. (2021) [34]	26 wk 3 mg/day	24	23	4 (8)	I: 42.7±11.3 C: 45.4±10.7	I: 111.4±25.5 C: 117.7±23.5	I: 123.8±20.1 C: 130.6±14.0	I: 37.5±6.9 C: 41.0±6.7	I: 130±24 C: 134±15	I: 92±23 C: 93±7	I: 5.5±0.6 C: 5.8±0.5	I: 120±11 C: 104±31

Values are expressed as number (%), mean±standard deviation, or median (interquartile range).
BMI, body mass index; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; I, intervention group; C, control group; NR, not reported.

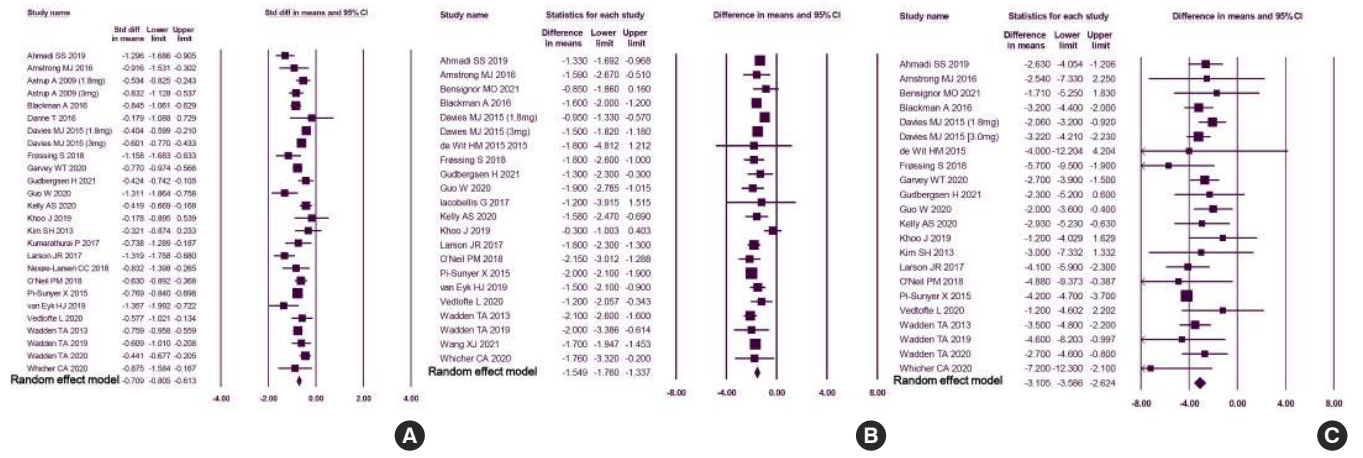

Fig. 2. Forest plots summarizing the effect of liraglutide on change of anthropometric data from baseline compared to placebo group. (A) Weight change (standard mean difference), (B) body mass index, (C) waist circumference (cm). CI, confidence interval.

in weight from the baseline and showed significantly decreased weight (MD, −4.16%; 95% CI, −4.90 to −3.43, I^2=72%). In the subgroup analysis according to the dosage of liraglutide, the subgroup with seven studies of liraglutide administered at 1.8 mg/day showed a significant reduction in body weight (MD, −4.04 kg; 95% CI, −4.61 to −3.47), and the subgroup with 12 studies with liraglutide administered at 3.0 mg/day showed a significant change in body weight (MD, −4.24 kg; 95% CI, −5.27 to −3.22) (Table 2). Subgroup analysis was conducted according to diabetic status. In studies conducted among nondiabetic participants, patients receiving liraglutide had a significantly larger reduction in weight from the baseline (MD, −4.47 kg; 95% CI, −5.38 to −3.51) than patients receiving placebo. Moreover, the patients with diabetes lost weight compared with the baseline weight (MD, −3.78 kg; 95% CI, −4.68 to −3.23) (Table 3).

Twenty one studies with 6,870 participants (liraglutide group 4,230; placebo group 2,640) reported BMI changes from the baseline [12-14,16-18,20,21,23,25,27-29,32-39]. BMI was significantly reduced in the liraglutide group compared with the placebo group (MD, −1.55; 95% CI, −1.76 to −1.34) (Fig. 2) with significant heterogeneity (I^2=71.4%). Since analysis with the funnel plot was asymmetric (Egger's test P=0.01), the trim-and fill method to adjust for publication bias was conducted. Three studies were imputed using the trim and fill method, but the significance was maintained (MD, −1.47; 95% CI, −1.69 to −1.26) (Supplemental Fig. S1). In sensitivity analysis, the significance of the results did not change even after each study was removed, and no outliers were observed (Supplemental Fig. S2). The subgroups receiving either liraglutide 1.8 or 3.0 mg/day showed a significant decrease in BMI (Table 2). The subgroup analysis according to the diabetes status showed that each subgroup had a significant reduction in BMI without heterogeneity (Table 3).

Twenty one studies with 7,437 participants (liraglutide group 4,509; placebo group 2,928) reported WC changes from the baseline [10-13,16-18,20,21,25,27-30,32-34,36-39]. The WC was significantly reduced in the liraglutide group compared with the placebo group (MD −3.11 cm; 95% CI, −3.59 to −2.62) (Fig. 2) without significant heterogeneity among the studies (I^2=34.3%). The funnel plot was symmetrical, and publication bias was not detected (Egger's test P=0.14) (Supplemental Fig. S1). The MD was significant even when each study was removed from the sensitivity analysis, and no outliers were observed (Supplemental Fig. S2). In the subgroup analysis according to the dosage of liraglutide, the subgroup with 10 studies with the administration of liraglutide at 1.8 mg/day showed a significant reduction in WC (MD, −2.55 cm; 95% CI, −3.21 to −1.89), and the subgroup with 12 studies of liraglutide administration at 3.0 mg/day also showed a significant change in WC (MD, −3.39 cm; 95% CI, −3.93 to −2.85) (Table 2). In the subgroup analysis by diabetes status, patients receiving liraglutide had a significantly larger reduction in WC from baseline than patients receiving placebo in the subgroups without or with diabetes mellitus (DM) (patients without DM: MD, −3.96 cm; 95% CI, −4.37 to −3.54; and patients with: MD, −2.61 cm; 95% CI, −3.14 to −2.07) (Table 3).

Effect of liraglutide on cardiometabolic parameters

Twenty-one studies with 7,529 participants (liraglutide group

Table 2. Meta-Analyses of the Effect of Liraglutide on Change of Anthropometric Data and Cardiometabolic Parameters from Baseline Compared to Placebo Group According to the Dosage of Liraglutide

Dosage of liraglutide	1.8 mg/day			3.0 mg/day		
outcome	No.	MD (95% CI, I^2)	Reference	No.	MD (95% CI, I^2)	Reference
Weight, kg	10	–4.04 (–4.61 to –3.47, 0%)	[14,17,20-22,30,31,33,38,39]	12	–4.24 (–5.27 to –3.22, 75.4%)	[12,13,16-19,24,25,28,31,32,34]
BMI, kg/m^2	11	–1.38 (–1.60 to –1.16, 14.2%)	[14,17,20,21,23,27,29,33,36,38,39]	11	–1.66 (–1.92 to –1.39, 73.1%)	[12,13,16,18,25,27,28,32,34,35,37]
Waist circumference, cm	10	–2.55 (–3.21 to –1.89, 0%)	[17,20,21,27,29,30,33,36,38,39]	12	–3.39 (–3.93 to –2.85, 30.5%)	[10-13,16,18,25,27,28,34,37]
Blood pressure, mm Hg						
Systolic blood pressure	11	–2.73 (–4.03 to –1.42, 0%)	[20-23,26,27,29-31,33,34,39]	12	–2.87 (–3.42 to –2.33, 0%)	[10-13,18,24,25,27,28,31,32,34]
Diastolic blood pressure	11	–0.30 (–1.21 to 0.62, 0%)	[20-23,26,27,29-31,33,39]	12	–0.73 (–1.12 to –0.34, 0%)	[10-13,18,24,25,27,28,31,32,34]
HbA1c, %	11	–0.61 (–0.83 to –0.38, 92.1%)	[14,20-23,26,27,29,33,38,39]	10	–0.27 (–0.36 to –0.18, 93.3%)	[10-13,18,24,25,27,28,32]

MD, mean difference; CI, confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin.

Table 3. Meta-Analyses of the Effect of Liraglutide on Change of Anthropometric Data and Cardiometabolic Parameters from Baseline Compared to Placebo Group According to Diabetic Status

Dosage of liraglutide	Without DM			With DM		
outcome	No.	MD (95% CI, I^2)	Reference	No.	MD (95% CI, I^2)	Reference
Weight, kg	10	–4.47 (–5.38 to –3.56, 69.7%)	[13,18-20,24,25,28,30-32]	4	–3.78 (–4.68 to –3.23, 0%)	[14,17,22,38]
BMI, kg/m^2	7	–1.88 (–2.05 to –1.72, 29.6%)	[13,18,20,25,28,32,35]	7	–1.32 (–1.53 to –1.12, 10.2%)	[14,17,23,27,29,38]
Waist circumference, cm	8	–3.96 (–4.37 to –3.54, 0%)	[11,13,18,20,25,28,30,32]	6	–2.61 (–3.14 to –2.07, 0%)	[10,17,27,29,36,38]
Blood pressure, mm Hg						
Systolic blood pressure	10	–2.82 (–3.41 to –2.34, 0%)	[11,13,18,20,24,25,28,30-32]	6	–3.20 (–4.39 to –2.01, 0%)	[10,22,23,26,27,29]
Diastolic blood pressure	10	–0.82 (–1.25 to –0.40, 0%)	[11,13,18,20,24,25,28,30-32]	6	–0.56 (–1.34 to 0.21, 0%)	[10,22,23,26,27,29]
HbA1c, %	8	–0.20 (–0.25 to –0.14, 72.4%)	[11,13,18,20,24,25,28,32]	8	–0.73 (–0.89 to –0.58, 73.2%)	[10,14,22,23,26,27,29,38]

DM, diabetes mellitus; MD, mean difference; CI, confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin.

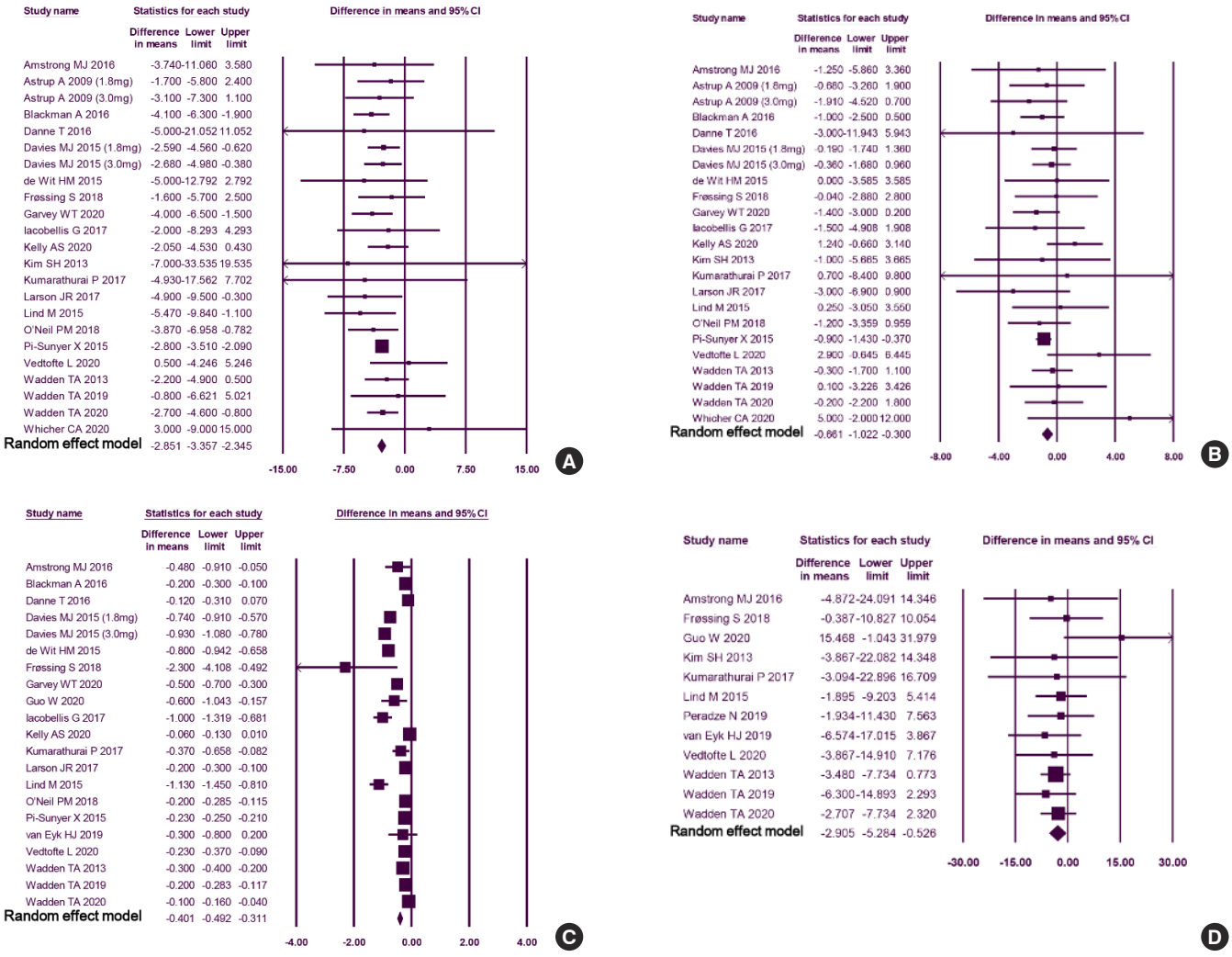

Fig. 3. Forest plots summarizing the effect of liraglutide on change of cardiometabolic parameters from baseline compared to placebo group. (A) Systolic blood pressure (mm Hg), (B) diastolic blood pressure (mm Hg), (C) glycated hemoglobin (%), (D) low-density lipoprotein cholesterol (mg/dL). CI, confidence interval.

4,622; placebo group 2,907) reported changes in blood pressure from the baseline (Fig. 3) [10-13,17,20-34,39]. Liraglutide significantly lowered blood pressure without significant heterogeneity (systolic blood pressure: MD, −2.85 mm Hg; 95% CI, −3.36 to −2.35; I^2=0%; and diastolic blood pressure: MD, −0.66 mm Hg; 95% CI, −1.02 to −0.30; I^2=0%) (Fig. 3). The funnel plot was symmetrical, and no publication bias was detected (systolic blood pressure, Egger's test P=0.91; diastolic blood pressure, Egger's test P=0.21) (Supplemental Fig. S1). The significance of these results did not change even after each study was removed in the sensitivity analysis (Supplemental Fig. S2). In the subgroup analysis according to the dosage of liraglutide, the subgroup with 11 studies with a liraglutide dosage of 3.0 mg/day showed a significant reduction in systolic blood pressure (MD, −2.87 mm Hg; 95% CI, −3.42 to −2.33) (Table 2), and the subgroup with nine studies with a liraglutide dosage of 1.8 mg/day also showed a significant reduction in systolic blood pressure (MD, −2.72 mm Hg; 95% CI, −4.03 to −1.42). In the subgroup analysis according to the diabetes status, both subgroups among patients receiving liraglutide had a significant reduction of systolic blood pressure (Table 3). Diastolic blood pressure was significantly reduced only in the subgroup that received 3.0 mg liraglutide/day or in the subgroup without DM (Tables 2, 3).

Twenty studies with 7,271 participants (liraglutide group 4,452; placebo group 2,819) reported changes in HbA1c (Fig. 3) [10-14,18,20-29,32,33,38,39]. Liraglutide significantly lowered HbA1c, although there was significant heterogeneity (MD,

Table 4. Adverse Events

Adverse event	Prevalence of adverse event		Odds ratio (95% CI)	Heterogeneity (I^2), %	Reference
	Liraglutide	Placebo			
Serious adverse events	6.1 (279/4,587)	5.6 (155/2,759)	1.10 (0.89–1.36)	0	[10-13,18,19,21,23-28,31,33,34,36-38]
Treatment withdrawal due to adverse events	9.0 (429/4,777)	3.6 (106/2,916)	2.44 (1.95–3.06)	0	[1,10-13,16,18-20,23-26,29-31,33,36,37,41]
Gastrointestinal adverse events	67.4 (1,368/2,031)	43.9 (639/1,454)	2.99 (2.57–3.47)	48.8	[10-13,18,19,24-26,30,31,33,38,41]
Nausea	39.4 (1,849/4,689)	14.2 (406/2,859)	4.00 (3.53–4.53)	41.1	[1,10-13,15,16,18,20,21,25,26,30-33,36,41]
Diarrhea	20.4 (958/4,689)	10.9 (312/2,859)	2.13 (1.85–2.46)	0	[1,10-13,15,16,18,20,21,25,26,30-33,36,41]
Vomiting	16.1 (741/4,610)	4.6 (127/2,785)	4.03 (3.30–4.93)	12.4	[1,10-13,15,18,20,21,25,30-33,36,41]
Abdominal pain	6.8 (277/4,071)	4.7 (111/2,387)	1.62 (1.28–2.06)	43.9	[1,10-13,15,16,20,21,30,32,33,36,41]
Hypoglycemia	36.7 (478/1,303)	26.0 (237/910)	1.66 (1.32–2.09)	38.6	[10,11,18,21,24,32,36]

Values are expressed as percentage (number/total number).
CI, confidence interval.

−0.40%; 95% CI, −0.49 to −0.31; I^2=93.2%) (Fig. 3). The funnel plot was asymmetrical, and significant publication bias was found (Egger's test P=0.03) (Supplemental Fig. S1). One study was imputed using the trim and fill method, but the significance was maintained (MD, −0.40%; 95% CI, −0.49 to −0.31). The significance of the results did not change following removal of each study in the sensitivity analysis, and no outliers were observed (Supplemental Fig. S2). In the subgroup analysis according to the dosage of liraglutide, the subgroup with 10 studies with a liraglutide dosage of 3.0 mg/day showed a significant reduction in HbA1c (MD, −0.27%; 95% CI, −0.36 to −0.18) (Table 2), and the subgroup with 11 studies of liraglutide dosage at 1.8 mg/day also showed a significant reduction in HbA1c (MD, −0.61%; 95% CI, −0.83 to −0.38). Among patients with diabetes, the HbA1c decreased by 0.73% (95% CI, −0.89 to −0.58) compared with the placebo group. Furthermore, improvements in HbA1c were greater in studies in patients with diabetes than in studies among patients without diabetes (MD, −0.20%; 95% CI, −0.25 to −0.14) (Table 3).

Twelve studies with 1,369 participants (liraglutide group 693; placebo group 676) reported changes in LDL-C concentration (mg/dL) from the baseline [11,13-15,20,22,26,30,32,33,38,39]. The MD between the liraglutide group and the placebo group using a random effects model was –2.91 mg/dL (95% CI, −5.28 to −0.53) without significant heterogeneity (I^2=0%). The funnel plot was symmetrical, and publication bias was not detected (Egger's test P=0.44) (Supplemental Fig. S1). In sensitivity analysis, the significance of the results did not change even after each study was removed, and no outliers were observed (Supplemental Fig. S2). Six studies with 5,481 participants (liraglutide group 3,535; placebo group 1,946) reported percentage changes in LDL-C concentration (%) from baseline and showed a significant reduction in LDL-C concentration (MD, −0.87%; 95% CI, −1.17 to −0.56) [27].

Safety of liraglutide

Among 4,587 participants with liraglutide in 19 studies [10-13,18,19,21,23-28,31,33,34,36-38], 279 (6.1%) had serious adverse event (Table 4). However, the risk in the liraglutide group for serious adverse event was not significantly higher than that of the placebo group (odds ratio [OR], 1.10; 95% CI, 0.89 to 1.36; I^2=0%). In 20 studies with 4,777 participants, 429 (9.0%) discontinued the treatment due to adverse events [1,10-13,16,18-20,23-26,29-31,33,36,37,41].

In 14 studies with 3,485 participants (liraglutide group 2,031; placebo group 1,454) [10-13,18,19,24-26,30,31,33,38,41], participants who received liraglutide had a significantly higher risk of gastrointestinal symptoms than those in the placebo group (OR, 2.99; 95% CI, 2.57 to 3.47; I^2=48.8%). The risk of the liraglutide group for hypoglycemia was significantly higher than that of the placebo group (OR, 1.66; 95% CI, 1.32 to 2.09; I^2=38.6%) [10,11,18,21,24,32,36].

DISCUSSION

In this meta-analysis of 31 studies, liraglutide therapy showed a significant association with body weight change. Overweight and obese people treated with liraglutide showed reduced body

weight and decreased WC compared with those treated with placebo. Moreover, liraglutide reduced both systolic and diastolic blood pressure, improved glucose tolerance, and improved dyslipidemia.

Since the FDA approved liraglutide as a long-term anti-obesity drug in 2014, researchers have analyzed the clinical outcomes of liraglutide and compared its benefits to other anti-obesity drugs. In 2016, Khera et al. [5] compared the weight loss efficacy of five FDA approved drugs in 28 clinical trials by meta-analysis. The primary outcome of the study was the proportion of participants who achieved at least 5% weight loss at 1 year [5]. They reported that liraglutide was one of the two most effective weight loss drugs (liraglutide: average 5.3 kg weight loss at 1 year compared with placebo) [5]. The most effective drug was phentermine-topiramate (average 8.8 kg loss at 1 year). Both of these drugs are appetite suppressants. A recent long-term follow-up study reported that liraglutide also led to sustained weight loss. A 3-year clinical trial reported that participants receiving liraglutide maintained reduced body weight at 3 years [34]. After 5 years, patients with type 2 diabetes mellitus (T2DM) receiving liraglutide showed significantly reduced body weight (−5.3±6.4 kg) [42].

Liraglutide has also shown significant improvements in cardiovascular outcomes in T2DM patients. The Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes (LEADER) trial (Clinicaltrials.gov NCT01179048) reported that liraglutide reduced major cardiovascular outcomes (hazard ratio, 0.85; 95% CI, 0.73 to 0.99) in T2DM patients with myocardial infarction/stroke history [43]. Furthermore, liraglutide reduced the composite risk of heart failure (HF) hospitalization or cardiovascular death in T2DM patients with and without HF (hazard ratio, 0.92; 95% CI, 0.74 to 1.15) and those without a history of HF (hazard ratio, 0.77; 95% CI, 0.65 to 0.91) [44].

In patients without diabetes, liraglutide does not reduce the cardiovascular disease risk. The Satiety and Clinical Adiposity-Liraglutide Evidence (SCALE) clinical trial reported that 3.0 mg liraglutide had no significant association with the composite outcome of first occurrence of cardiovascular death, nonfatal myocardial infraction, or nonfatal stroke (hazard ratio, 0.70; 95% CI, 0.20 to 2.50) [41]. Although that study did not prove the benefits of liraglutide on major cardiovascular outcomes, this meta-analysis showed the possible cardiovascular benefits of liraglutide in nondiabetic individuals. Liraglutide treatment significantly reduced both systolic and diastolic blood pressures and LDL-C in nondiabetic participants.

The underlying mechanism of body weight reduction by liraglutide mainly depends on appetite suppression and delayed gastric emptying by GLP-1 [7]. The half-life of natural GLP-1 in the circulation is less than 2 minutes [7]. The enzyme dipeptidyl peptidase-4 degrades GLP-1, and the kidneys rapidly clear the remnant metabolites [45]. To overcome this limitation, liraglutide was created by substituting an amino acid and adding a fatty acid chain [45]. The half-life of liraglutide is 13 hours, which means that once-daily subcutaneous administration is sufficient to control the glucose levels of people with diabetes and to reduce the appetite of obese individuals [45].

GLP-1 receptor agonists have shown non-inferiority for cardiovascular outcomes of T2DM patients in seven recent clinical trials; Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA); LEADER; Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN-6); Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL); Harmony outcomes study; Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND); and Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 trials [46]. Among these clinical trials, GLP-1 receptor agonists showed significant cardiovascular benefits in two trials (liraglutide in the LEADER trial and semaglutide in SUSTAIN-6) [46]. Liraglutide improved cardiovascular outcomes in T2DM patients (hazard ratio, 0.87; 95% CI, 0.78 to 0.97) over a 3.8-year median follow-up [46,47]. Semaglutide is a new, long-acting GLP-1 receptor agonist, which allows for weekly subcutaneous injection [48]. Moreover, semaglutide improved cardiovascular outcomes in T2DM patients (hazard ratio, 0.74; 95% CI, 0.58 to 0.95) during a 2.1-year median follow-up [46,49].

This meta-analysis provides supporting evidence of the cardiovascular benefits of GLP-1 receptor agonists. The underlying cardioprotective mechanisms of liraglutide depend on both direct and indirect actions in multiple organs. GLP-1 receptor agonists have direct effects on the heart, as well as broader antidiabetic and anti-obesity effects [50]. GLP-1 reduces cardiac inflammation in mice receiving a high-fat diet and reduced the infarct size in a mouse myocardial infarction model [51]. In animal studies and human clinical trials, GLP-1 receptor agonists have resulted in improved lipid profiles, reduce fat inflammation, and induce natriuresis in the kidney [51,52].

This meta-analysis show that liraglutide treatment reduced the LDL-C levels of the participants. This improvement may be the result of body weight reduction and improved glucose control by liraglutide treatment [52]. Recent papers reported that GLP-1 receptor agonism directly modulates hepatic cholesterol metabolism by suppressing adenosine triphosphate-binding cas-

sette transporter A1 [53] and regulating intestinal lipid and lipoprotein metabolism [54]. These direct effects of GLP-1 are other possible mechanisms of lipid lowering effects of liraglutide.

This study had some limitations. First, we could not evaluate the direct benefits of liraglutide use on the major cardiovascular outcomes of participants. Although, we identified enough data related to cardiovascular parameters and calculated the beneficial effects of liraglutide use on these parameters, there are enough clinical studies about cardiovascular events after liraglutide use. Second, we could not analyze important blood parameters related to obesity and cardiometabolic dysfunctions, such as adiponectin, leptin, and inflammatory markers, because of lack of data. Further long-term follow-up clinical trials are needed to overcome these limitations.

In conclusion, liraglutide is a very effective treatment for overweight and obese individuals for body weight reduction and sustained weight loss. Furthermore, this therapy improves cardiometabolic parameters during treatment. Additional long-term clinical studies are needed to confirm the cardioprotective role of liraglutide in nondiabetic individuals.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: S.M., S.H.Y., C.M.O. Acquisition, analysis, or interpretation of data: S.M., J.L., Y.J.K., C.M.O. Drafting the work or revising: S.M., H.S.C., S.H.Y., C.M.O. Final approval of the manuscript: S.M., H.S.C., J.M.Y., S.H.Y., C.M.O.

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