EFFECTIVENESS OF GLP-1RA ON WEIGHT REDUCTIONS IN OVERWEIGHT OR OBESITY PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF REAL-WORLD DATA

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ABSTRACT

The effectiveness of Glucagon-like peptide-1 receptor agonist (GLP-1ra) in reducing weight in overweight or obese patients is still controversial. This systematic review and meta-analysis aimed to compare the effect of GLP-1ra in reducing weight with alternative treatments for obesity or antidiabetic medications. The related studies were identified from MEDLINE and Scopus databases since initial to July 2023. Cohort studies which compared weight reduction between patients who received GLP-1ra and other treatments for obesity (i.e., Exenatide, Liraglutide, Semaglutide, Dulaglutide) or antidiabetic medications (i.e., Sodium glucose cotransporter 2 inhibitors (SGLT2i), Basal Insulin Supported Oral Therapy (BOT)) were included. Data were independently extracted by 2 independent reviewers. Four cohorts with 1,223 patients were met inclusion criteria. The mean difference of weight reduction between 2 groups were estimated and pooled using direct meta-analysis. The results revealed GLP-1ra over other treatments in reducing body weight, with a mean difference (MD) of -2.46 (95% CI, -5.44 to 0.52, p = 0.11) with high heterogeneity (I^2 = 91.75%). It means that GLP-1ra can lose weight 2.46 kg higher than comparator but not statistically significant. A sensitivity analysis was performed by excluding a study in intervention (SGLT2) and percentage of female, reduced heterogeneity to I2= 31.47%, and confirmed that GLP-1ra was significantly higher weight reduction about 3.78 kgs. (MD = -3.78; 95% CI, -5.23 to -2.33, p = 0.00) than other treatments of obesity.

Keywords: Systematic Review, Meta-analysis, GLP-1 Receptor Agonists, GLP-1ra, Weight Reduction, Obesity, Overweight, Type 2 Diabetes, Comparative Effectiveness

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INTRODUCTION

In 2022, global overweight and obesity rates reached alarming levels. Approximately 2.5 billion adults aged 18 years and older were overweight, with over 890 million living with obesity (World Health Organization, 2023). This marked a significant increase from 1990, with prevalence varying across regions. Additionally, there were an estimated 37 million overweight children under 5 years old, showing a rise in low- and middle-income countries. Over 390 million children and adolescents aged 5-19 years were overweight, with prevalence increasing dramatically from 8% in 1990 to 20% in 2022. The number of obese children and adolescents also surged, reaching 8% by 2022, totaling 160 million individuals.

Obesity increases the risk of developing type 2 diabetes (T2D) due to its role in promoting insulin resistance and impairing blood sugar control (Lin & Li, 2021). The coexistence of obesity and T2D poses a growing global public health challenge, with millions affected and heightened risks of severe complications such as cardiovascular issues, kidney problems, and neuropathy. This complex issue necessitates comprehensive interventions to promote healthier lifestyles and equitable healthcare access to address its pervasive impact.

Effective management of overweight and obesity involves adopting a balanced diet rich in fruits, vegetables, lean proteins, and whole grains while limiting sugary and high-fat foods (Shoemaker et al., 2022), alongside regular aerobic and strength training exercises (Pojednic et al., 2022). However, while dietary control and physical activity can lead to weight loss of 1-6 kgs, maintaining its long-term is challenging. For severe cases, bariatric surgery (Linke et al., 2020) or weight-loss devices like electrical stimulation are options. Medications such as Orlistat, Phentermine, Methamphetamine, and Glucagon-like peptide-1 receptor agonist (GLP-1ra) (Chakhtoura et al., 2023) are available, with GLP-1ra recommended for overweight or obese patients due to its ability to lower glucose levels and reduce body weight through mechanisms like increasing insulin secretion and suppressing glucagon secretion (Nauck et al., 2021).

LITERATURE REVIEWS

There was one systematic review and meta-analysis (SRMA) of 3 randomized controlled trials (RCTs) and 3 observational study focus on weight loss in adult with obesity. They compare GLP-1ra with bariatric surgery (Sarma & Palcu, 2022), a standard intervention for severe obesity. It consistently demonstrated significant higher weight loss in bariatric surgery than GLP-1ra, averaging approximately mean difference (MD) of -22.68 kg in RCT and -25.11 kg in observational study, respectively. Bariatric surgery also led to substantial reductions in body mass index (BMI), suggesting its effectiveness in inducing weight loss, as observed across both RCTs and observational studies.

Another SRMA of RCT focused on assessing GLP-1ra's efficacy in weight loss versus placebo among obese individuals without diabetes mellitus (Iqbal et al., 2022). Drawing on data from 12 RCTs involving a sizable participant cohort, it highlighted the significant advantage of GLP-1ra over placebo in promoting weight reduction. The findings revealed an average weight loss difference of -7.1 kgs (95% CI, -9.2 to -5.0) between GLP-1ra groups and control groups.

Furthermore, a systematic review employing network meta-analysis methodology compared GLP-1ra with sodium glucose co-transporter type 2 inhibitors (SGLT2i) in weight reduction among overweight or obese patients (Ma et al., 2023), irrespective of diabetes status. The findings showcased substantial reductions in body weight between GLP-1ra and SGLT2i. These results provided valuable insights into the efficacy of GLP-1ra compared to other interventions, aiding in informed decision-making for the management of obesity among diverse patient populations.

However, the results from SRMA or MA of RCTs might not be compatible with those from real-world studies. The confounding effects needed to be considered when comparing

treatment effects in real-world studies. Up to now, several observational studies compared the effectiveness of GLP-1ra with obesity treatment and other glucose-lowering agents by applied conventional multivariate regression models to deal with confounding effects were published (Gorgojo-Martínez et al., 2019; Grabarczyk & Wissman, 2020; Overbeek et al., 2018; Valladales-Restrepo et al., 2023; Wu et al., 2022). Therefore, we conducted a SRMA of non-RCT to estimate the treatment effectiveness on weight reduction between GLP-1ra and obesity treatments or other glucose-lowering drug agents in over-weight or obesity patients.

RESEARCH METHODOLOGY

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses. (PRISMA) (Page et al., 2021)

Databases and search engines

All related articles were identified from online database PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/), from inception to July 2023. The search terms and strategies were constructed based on population (overweight or obesity patients), intervention (GLP1ra), comparator (obesity treatments or antidiabetic drugs), and outcome (weight reduction).

Selection of studies

Public studies were independently selected by reviewers (C.A. and O.M.) using the information from the title and abstract. Full articles were reviewed if a decision could not be made based on the abstracts. Disagreements were resolved by discussion with supervisors (S.R., T.A., and A.T.).

Data extraction

Data were extracted by 2 independent reviewers (C.A. and O.M.) using a data extraction form which consist of participant baseline characteristics (i.e., sex, age, weight, HDL, LDL, cholesterol, and comorbidities), type of GLP-1ra (i.e., drug name, and duration), type of obesity treatment (i.e., medication type, dosage, duration, and frequency), type of T2D treatment (Orlistat), type of outcomes (continuous). Data for pooling (i.e., the number of sample sizes, mean, standard deviation (SD), mean difference with confidence interval (CI) for continuous outcomes) were extracted for the purposes of conducting meta-analyses.

Risk of bias assessment

In our study, we conducted a comprehensive assessment of bias, considering various domains, including Selection Bias, Performance Bias, Detection Bias, Attrition Bias, and Reporting Bias. To ensure the rigor and consistency of our bias assessment, we employed the 'The Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I)'(Sterne et al., 2016) assessment tool. A detailed description of the ROBINS-I assessment tool, including its criteria and guidelines for evaluating bias across these domains, was provided in the Appendix of this study. This systematic approach allowed us to thoroughly evaluate the potential sources of bias and enhance the reliability of our research findings.

Statistical analysis

A pairwise meta-analysis was performed on the comparison of reduction of weight between GLP-1ra and obesity treatments or glucose-lowering drug agents, if there were at least 3 studies available. Adjusted mean differences, along with 95% confidence intervals (CI) were pooled across studies. A random-effect model using the DerSimonian-Laird method was employed if heterogeneity was present; otherwise, a fixed-effect model by inverse-variance method would have been used.

Heterogeneity across studies was examined through the I^2 statistic and evaluated using the Cochran's Q test. I^2 was classified as low, moderate, or high if it was < 25%, 25-74%, and ≥ 75%, respectively, with particular attention given to moderate degrees or higher ($I^2 \geq 25\%$) to account for between-study variations in pooling.

Potential sources of heterogeneity were explored by fitting each covariate, including mean age, percentage of gender, mean weight, mean HbA1c, mean fasting blood sugar, mean HDL, mean LDL, and percentage of comorbidities (i.e., T2D, HT, CVD, CKD, OSA, DLP), into a meta-regression model if data were available. A covariate was considered as a source of heterogeneity if the results of the meta-regression indicated a decrease in τ^2 of more than 50%. Publication bias was assessed using Egger's test and a funnel plot, with significance indicated by a P-value < 0.05 or funnel plot asymmetry. Further analysis of asymmetry was conducted using a contour-enhanced funnel plot, categorizing in significant and non-significant areas in order to determine cause of asymmetry whether by publication bias.

RESEARCH RESULTS

Study selection

The PRISMA flow was shown selection process (Figure.1). Literature databases using through search terms uncovered 807 studies in total, with 300 from PubMed and 507 from Scopus. After eliminating 230 duplicate studies, 577 remained for title and abstract screening. Out of these, 573 were excluded, leaving only 4 that met the inclusion criteria (Gorgojo-Martínez et al., 2019; Grabarczyk & Wissman, 2020; Overbeek et al., 2018; Valladales-Restrepo et al., 2023).

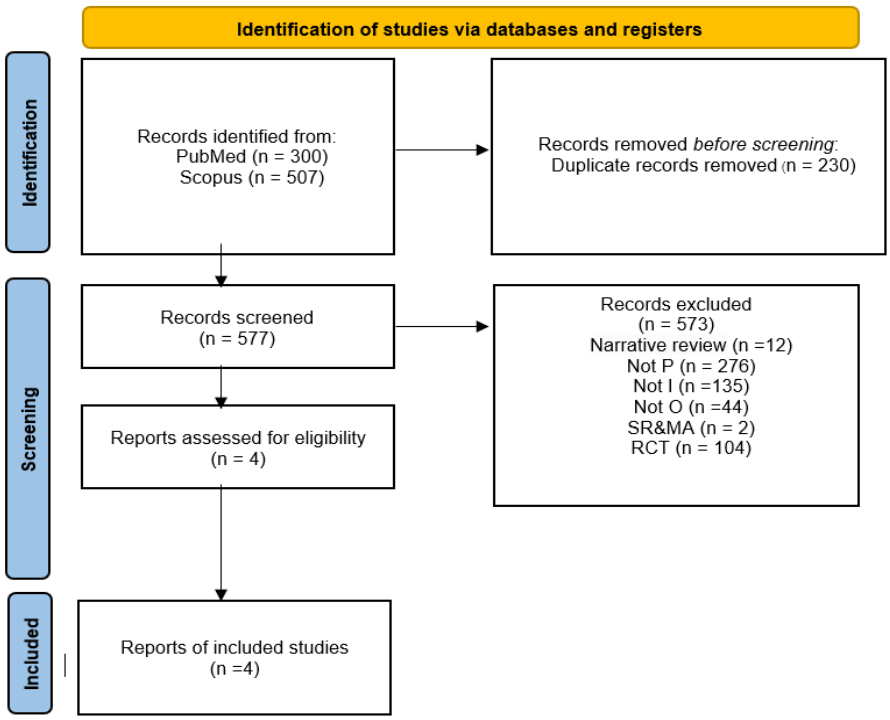

Figure 1 PRISMA Flow diagram

Characteristic of included study

This review included 4 cohort studies published from 2018 to 2023 which 1,223 overweight or obese patients. Characteristics of patients were described in Table 1. Two studies compared GLP-1ra with obesity treatments (orlistat). Other 2 studies compare GLP-1ra with glucose-lowering drug agents (emplazliphozin and BOT). The duration of intervention ranged from 7 to 12 months and mean patients age ranged from 46 to 65 years. Percentage of Female from 5 to 80.

Table 1 Characteristics of patients, and treatments of included studies

Author,Year	Intervention	Duration of treatment (Month)	Weight at baseline (Mean)	Sex (%)	Age (Mean)	SBP	DBP	TC	LDL	HDL	HT
Gorgojo-Martínez, 2019	Liraglutide	7	108	73	52	-	-	-	-	-	44
	Orlistat		105	75	47	-	-	-	-	-	55
Grabarczyk, 2020	Liraglutide	12	118	5	63	-	-	157	85	37	94
	Emplazliphozin		110	6	65	-	-	156	84	37	94
Overbeek, 2018	Liraglutide	12	115	56	58	138	81	4	2	1	-
	BOT		108	55	61	138	81	5	3	1	-
Valladales-Restrepo, 2023	Liraglutide	12	102	71	47	116	73	151	79	50	62
	Orlistat		95	80	46	116	75	211	138	39	50

Note: TC: Total cholesterol, HT = Hypertension

Body weight

The pairwise meta-analysis showed that GLP-1ra had non-significant higher weight reduction than obesity treatments or other glucose-lowering drug agents with MD of -2.46; 95% CI, -5.44 to 0.52. and had high heterogeneity of I^2= 91.75% (Figure 2). Therefore, we conducted a sensitivity analysis by exclude one study (Grabarczyk, T. R., 2020) which compared GLP-1ra with glucose-lowering drug agent (SGLT2i). The results of comparision of weight reduction between GLP-1ra with other treatments (Orlistat and BOT) found a significantly greater decline in body weight in GLP-1ra with MD, -3.78; 95% CI, -5.23 to -2.33, p = 0.00. The heterogeneity was decrease (I^2 = 31.47%) after exclude study with comparator SGLT2i (Figure 3). Publication bias was assessed using a funnel plot and Egger's test (Figure 4). The funnel plot for overall pooling indicated that one study fell outside the range of the symmetrical funnel. The Egger test did not reveal significant evidence of asymmetry (coefficient = -3.94, SE = 4.31, p = 0.361). Additionally, the contour-enhanced funnel plot displayed asymmetry (Figure 5), with a signal of missing studies in the non-significant region (white region). Consequently, the asymmetry of the funnel plot was caused by publication bias and heterogeneity.

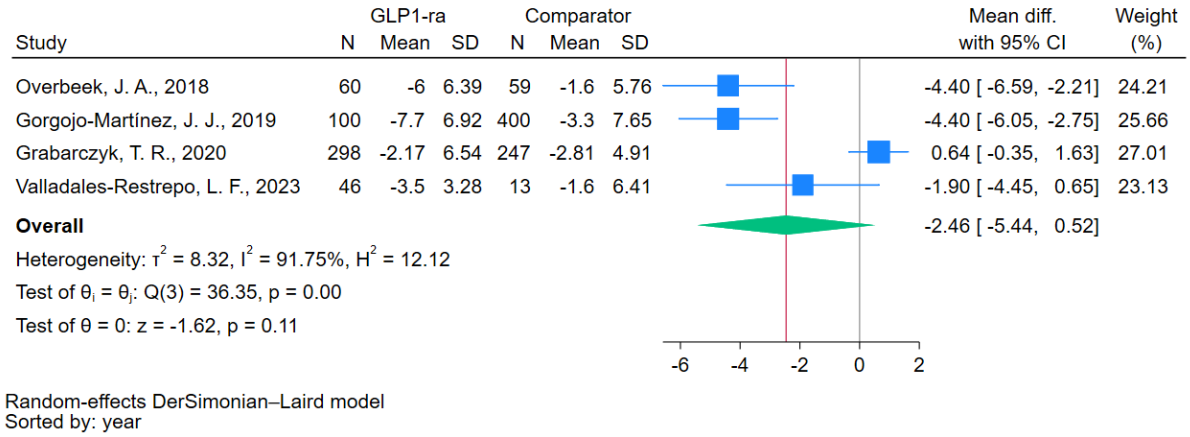

Figure 2 Forest plot of weighted mean difference from baseline.

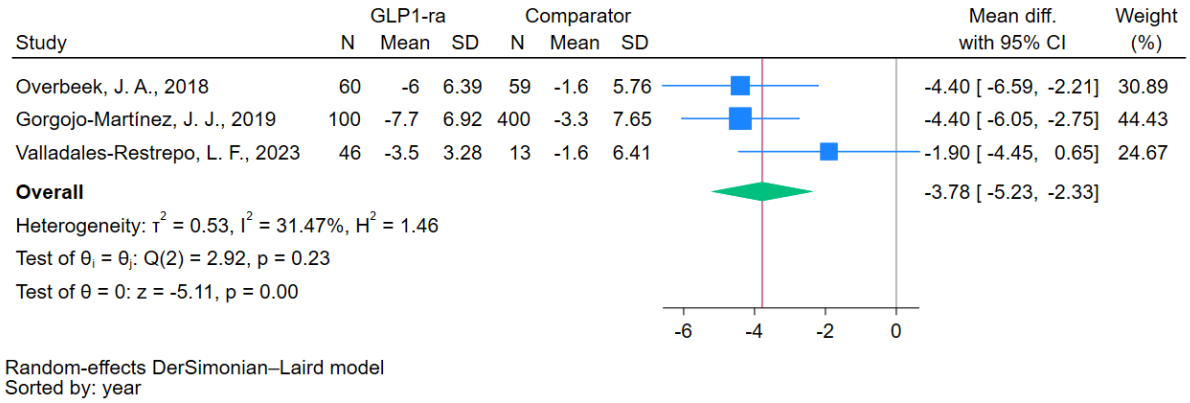

Figure 3 Forest plot of weighted mean difference from baseline after conducted a sensitivity analysis.

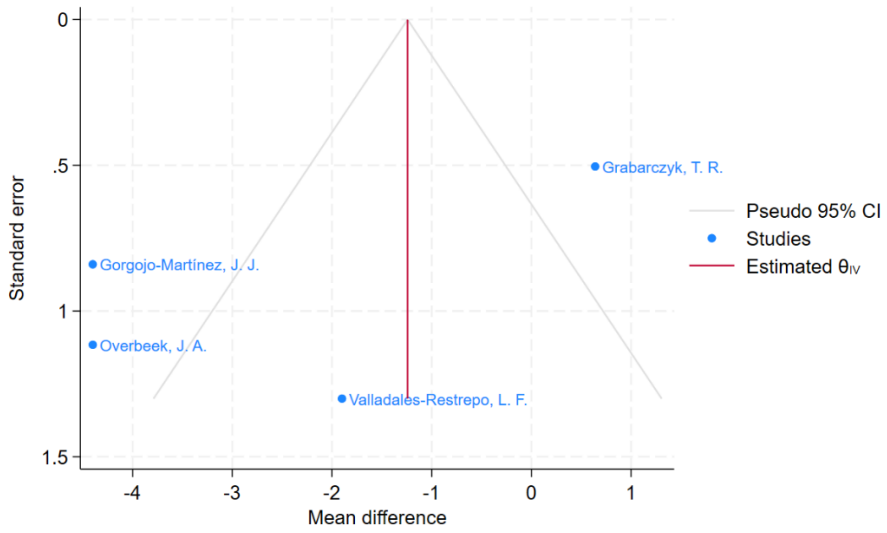

Figure 4 Funnel plot of GLP-1ra vs other treatments in the 4 studies assessed in the meta-analysis.

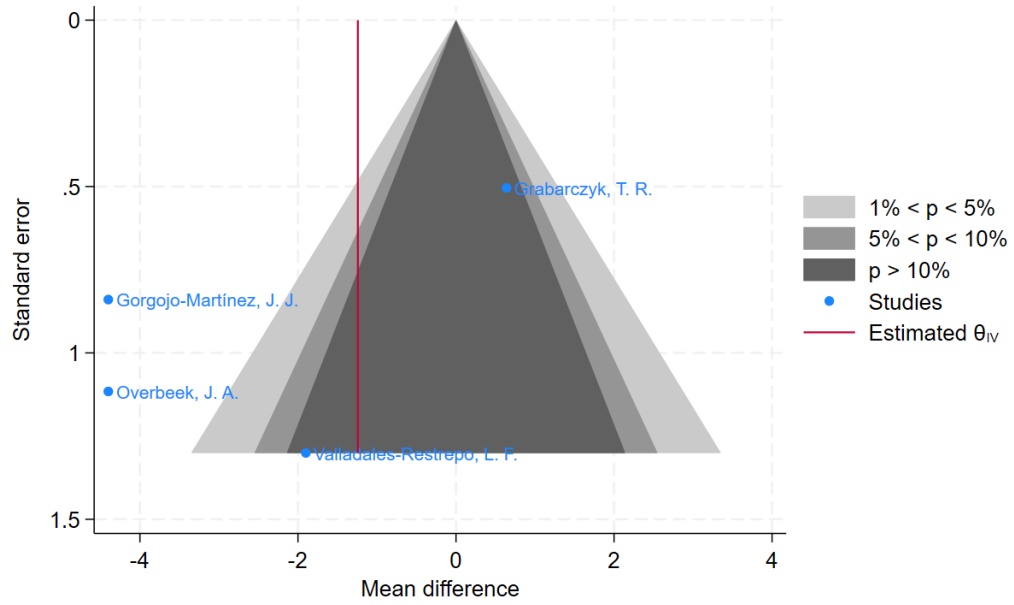

Figure 5 Contour-enhanced funnel plot of GLP-1ra vs other treatments.

DISCUSSION & CONCLUSION

The analysis indicated a significant advantage of GLP-1ra over alternative treatments in reducing body weight, aligning with previous research that underscores its efficacy in managing metabolic conditions. Nonetheless, the presence of substantial heterogeneity (I^2 = 91.75%) among the studies raises concerns about result consistency. This heterogeneity may stem from differences in study methodologies, patient demographics, or treatment regimens, prompting a deeper investigation into its underlying causes.

To address this issue, a sensitivity analysis was conducted, focusing on excluding the study conducted by Grabarczyk et al. (2020). The unique characteristics of Grabarczyk's study could have contributed to the observed heterogeneity. Specifically, Grabarczyk's study showed significant differences in intervention and percentage of female when compared to the other studies. After excluding Grabarczyk's study, the heterogeneity decreased significantly to I^2 = 31.47%. Despite this reduction, the sensitivity analysis continued to demonstrate a substantial and statistically significant decrease in body weight with GLP-1ra compared to alternative treatments. This indicates that the observed heterogeneity may not undermine the overall conclusion regarding the superiority of GLP-1ra in promoting weight loss, highlighting the robustness of the findings.

In conclusion, the findings from this analysis support the significant advantage of GLP-1ra in reducing body weight compared to other treatments among the studied population. Despite concerns about heterogeneity, the sensitivity analysis reaffirmed the robustness of this conclusion. Healthcare providers may consider GLP-1ra as a favorable option for patients aiming to achieve weight loss. However, further research is warranted to explore the underlying reasons for heterogeneity and to investigate the long-term effects and safety profile of GLP-1ra in diverse patient populations.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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