

Efficacy and Safety of GLP-1 Receptor Agonists in Adults with Overweight/Obesity: A Systematic Review

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Abstract

GLP-1 supplementation serves to mimic the physiological effects of the GLP-1 receptor agonist hormone produced naturally by the body. The primary functions of the GLP-1 hormone include blood glucose control, increased satiety, and managing blood pressure. Historically, the GLP-1 drug has been used in the treatment of type 2 diabetes mellitus (T2DM), but with the rise of the global obesity epidemic, use has been pivoted towards answering this worsening health challenge. This systematic review compiled an assortment of research studies geared towards assessing if GLP-1 treatment is a safe and effective method for weight loss in overweight and obese adults. The study outcomes included mean change in body weight, change in waist circumference, and the occurrence of adverse events. Following the literature review, the majority of studies contained results that would favor the overall safe use of the GLP-1 drug. GLP-1 usage was consistently associated with significant decreases in body mass and waist circumference alongside non-life-threatening adverse events. However, the incidence of adverse events among intervention groups was observed to be relatively high. With various health organizations (WHO, ADA, and AND) providing conditional guidelines concerning the GLP-1 drug, further research is warranted for stronger evidence and conclusions for overweight/obese populations.

Keywords: GLP-1, obesity, overweight, body weight, weight loss, waist circumference, adverse events

1. Introduction

Glucagon-like peptide 1, or GLP-1, is a hormone produced by the small intestine serving many functions in digestion, blood glucose control, and metabolism. When energy is consumed in the form of glucose, the pancreas releases insulin while also blocking the secretion of glucagon (Cleveland Clinic, 2025). Due to these functions, blood glucose levels remain at low levels, and the body better utilizes glucose for energy. Aiding in this, GLP-1s also delay gastric emptying in stomach, causing less glucose to be released from the food and into the bloodstream. The GLP-1 hormone additionally promotes satiety, diuresis, and natriuresis, thus also controlling blood pressure (Müller et al., 2019). Overall, GLP-1s serve as crucial hormones in the regulation of many systems within the body through their extensive digestive, glycemic, and metabolic effects.

GLP-1 agonist/analog medications imitate the effects of the naturally occurring hormone GLP-1 and have been approved and successful in the treatment of type 2 diabetes mellitus (T2DM). Traditionally, medications like metformin have been used to manage diabetes, although GLP-1s are being prescribed in place of metformin in various instances. The reasons for this substitution include poor drug efficacy, potential contraindications, or if one's HbA1c is above the target ($>7\%$) alongside other comorbidities such as chronic kidney disease, heart failure, or atherosclerosis (Cleveland Clinic, 2025). Apart from blood glucose control, one of the prominent risk factors and focuses of T2DM is obesity.

Overweight and obesity are defined as the abnormal or excessive accumulation of fat or adipose tissue and a BMI of 25 kg/m^2 - 29.9 kg/m^2 and 30 kg/m^2 or higher, respectively (Panuganti et al., 2025). Obesity is a complex disease with a multitude of etiologies that continues to grow every year. Overweight and obesity affect close to three billion people worldwide with obesity being one of the most widespread economic health burdens in the world (World Obesity, 2025). While obesity is a risk factor for several chronic diseases such as cardiovascular disease, diabetes mellitus, and certain cancers, research has shown that weight loss of just 5% - 10% can greatly improve health outcomes and lower risks (Panuganti et al., 2025; World Health Organization, 2025). The mainstay methods of weight loss in individuals with overweight and obesity typically include incorporating daily exercise, making lifestyle modifications, and eating a healthy and balanced diet. Although, in instances when traditional weight loss interventions are unsuccessful, the question remains whether medicinal approaches are safe and appropriate.

While GLP-1s have been approved for the treatment of T2DM, their use in patients with overweight and obesity is still being studied. There have been several clinical evaluations and trials to determine the effectiveness of various types of GLP-1s in obese patients with different observed outcomes, such as blood glucose, lipid profiles, and gastrointestinal functionality. The primary aim of this systematic review is to assess the safety and effectiveness of GLP-1s for weight loss in patients with overweight and obesity.

2. Method

This systematic review followed the framework of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Guidelines (Page et al., 2021). The PRISMA flow diagram, as shown in Figure 1, delineates the study selection process, including the initial database search, screening, and final inclusion of selected studies. The search, screening, extraction, and quality assessment were all conducted independently by one reviewer without any disagreements.

2.1 Protocol and Registration

This review was registered with the International Prospective Register of Systematic Reviews, PROSPERO (ID: 1086941) per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

2.2 Search Strategy

The original search was conducted and completed in June 2025, and a secondary search was conducted and completed in February 2026 following similar search criteria. The secondary search did not generate any newly published articles. Online databases utilized in this search were Embase, PubMed, Cochrane, and the Web of Science. The keywords to describe the population, intervention, and outcome for the search are outlined in Table 1. Each term was also considered as Medical Subject Headings (MeSH). Individual search strategies were used for each database to promote specificity and narrow down numbers. Utilized search strings included: “(Obesity OR Overweight) AND (Glucagon-Like Peptide 1 OR GLP-1) AND (Weight Loss)” and “(Obesity, Abdominal OR Obesity, Morbid) AND (GLP-1 OR Semaglutide) AND (BMI Reduction)”. Filters for full-text articles published between 2020 and 2025 in English were chosen alongside the filters for including only control trials, clinical studies, and clinical trials. Of the eligible studies, the methods sections were reviewed for inclusion and exclusion criteria during screening.

Table 1. Key search terms that were combined for the database search.

Population Key MeSH Terms	Intervention Key MeSH Terms	Outcome Key MeSH Terms
Obesity, Abdominal	Glucagon-Like Peptide 1	Weight Loss
Obesity, Morbid	GLP-1	BMI Reduction
Obesity	Semaglutide	
Overweight		

2.3 Eligibility Criteria

Selected studies from the original search met inclusion criteria outlining age, gender, country, health condition, intervention, outcome, study design, study group size, language, and publication year. The inclusion/exclusion criteria are outlined in Table 2. Randomized control trials, clinical studies, and clinical trials were included. Adults aged 18-65 years old were included with males and females from the United States, the United Kingdom, Australia, and China. While a handful of studies were found to be conducted in random, scattered countries throughout the world, their distribution remained too miscellaneous for this review. The vast majority of eligible studies were performed in the four main countries of the United States, the United Kingdom, Australia, and China, hence why they were chosen as the only countries for inclusion. Participants were required to be overweight (BMI >25 kg/m²) or obese (BMI >30 kg/m²) and must not have cardiovascular disease, chronic kidney disease, or be at a healthy weight or underweight. Interventions falling under any other type of GLP-1 were included although not specifically used as MeSH terms, such as liraglutide, tirzepatide, exantide, and dulaglutide. All other weight loss medications were not included. The criteria for the outcomes were any weight loss or reduction in BMI. Study groups of over ten subjects were included. Subjects with additional conditions such as pregnancy, breastfeeding, and

edema/ascites were excluded. Lastly, fully English studies within the last five years were required for inclusion.

Table 2. The inclusion and exclusion criteria utilized in selecting eligible studies.

Criteria	Inclusion	Exclusion
Age	Adults 18 – 65-years-old	<18-year-olds & >65-year-olds
Gender	Male or Female	N/A
Setting/Country	US, UK, Australia & China	Countries other than the US, UK, Australia & China
Health Status/Problem/Condition	Overweight/Obesity	CVD, CKD, underweight/healthy weight, pregnant women, breastfeeding women, individuals with edema/ascites
Intervention/Exposure	GLP-1s	Other weight loss drugs
Outcome	Weight Loss/Reduction, BMI, Adverse Events	N/A
Study Design Preferences	RCT, clinical trial, clinical study	Every other type of trial/study, systematic reviews
Size of Study Groups	>10 person groups	<10 person groups
Language	English	Any other language
Publication Year Range	Past 5 years	Longer than 5 years
Other (if applicable)	Any type of GLP-1	N/A

2.4 Study Selection

The PRISMA flow diagram (Figure 1) outlines the review search and selection process. Deduplication, screening, and full text assessment were performed using Rayyan© web tool (Rayyan, 2016). After the removal of duplicates, the screening process transitioned to filtering out studies based on the titles and abstracts. From there, a full text screening was completed on the remaining articles.

2.5 Data Extraction and Quality Assessment

From the included studies, data was extracted and inserted into a table adapted from the Evidence Analysis Manual (2022). The table was adapted to include the study purpose, study design, population, setting, intervention, results, conclusions, limitations of findings, and the quality grade. The intervention was reported as the specific type of GLP-1 (semaglutide, tirzepatide, etc.), and the outcomes were the same as or similar to the primary outcome of weight loss. Summary statistics included any significant outcome percentages or value changes.

The Academy of Nutrition and Dietetics' Quality Criteria Checklist (QCC) was used to assess

the methodological quality of each study (Academy of Nutrition and Dietetics, 2022). Both relevance and validity were evaluated in the form of ‘yes’ and ‘no’ questions with options for a lack of clarity. At the end of the checklist, a rating of positive (+), neutral (Ø), negative (-) is then selected. Finally, the strength of evidence is graded using a scale of: Grade I = good, Grade II = fair, Grade III = limited/weak, Grade IV = expert opinion only, and Grade V = not assignable.

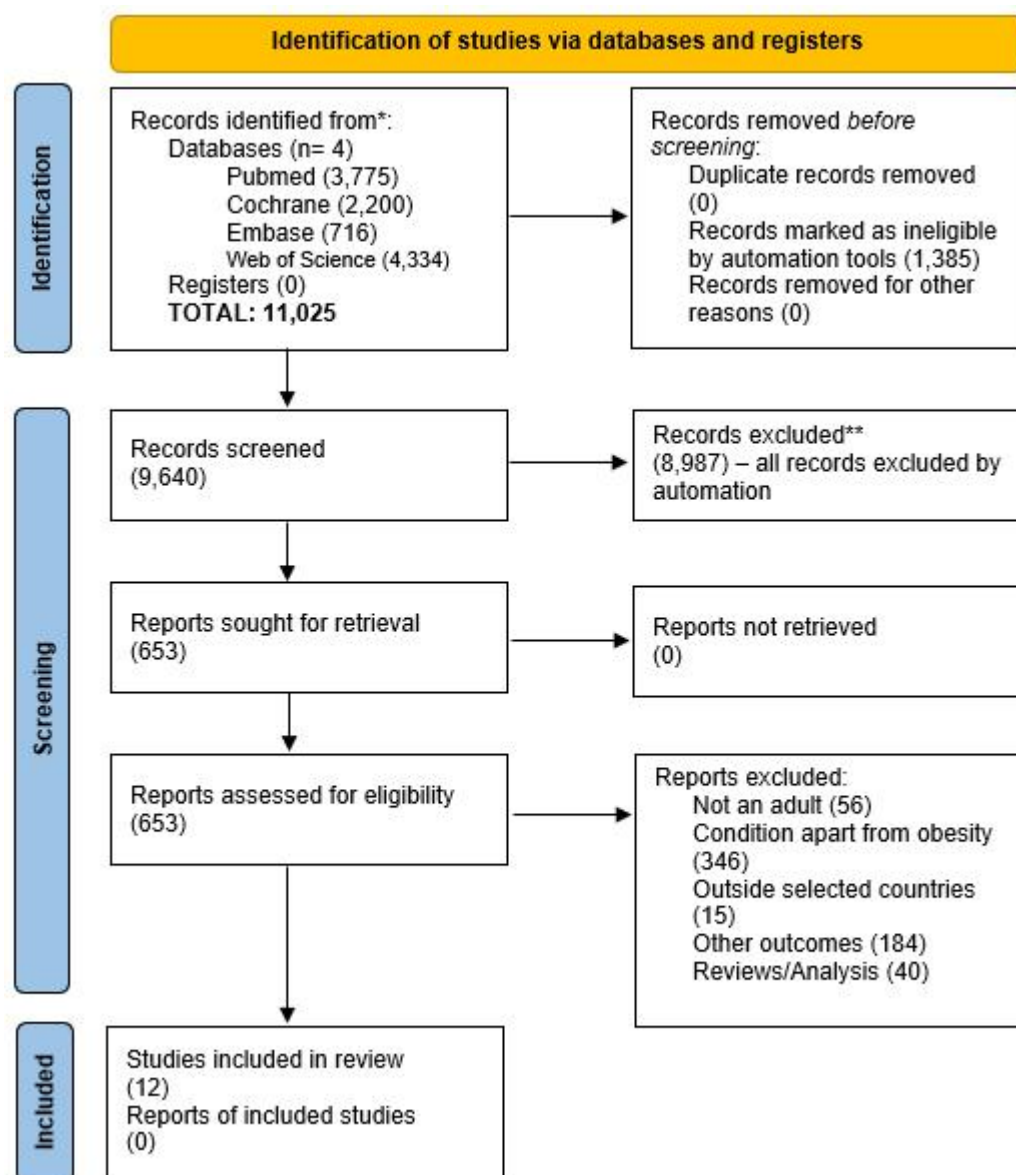


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart.

3. Results

As outlined in the PRISMA diagram, the literature search led to the inclusion of 12 total studies. Eleven thousand and twenty-five studies were originally found from the identified databases with 1,385 records removed prior to screening as an initial sweep by the automation tool’s eligibility requirements. From the 9,640 articles, 8,987 were excluded by the automation tool’s removal of duplicates, completed entirely and automatically by the

Rayyan© deduplication function. The remaining 653 articles were assessed individually by hand based on eligibility criteria, leading to the removal of 641 records. The exclusions were specifically due to studies without adults (56), populations with conditions other than overweight/obesity (346), singular/very few studies conducted in other countries (15), other outcomes (184), and review/analysis studies (40). Ultimately 12 studies were included for assessment and review.

Characteristics of participants across the studies remained relatively homogenous. Every study included both males and females with 11 of the 12 studies enlisting participants age >18 years old with one study requiring participants to be at least 30 years old. BMI ranges varied slightly, with one study allowing for BMIs >20 kg/m², three studies with BMIs >24 kg/m², six studies with BMIs >27 kg/m², and two studies with BMIs >30 kg/m². Five studies focused specifically on participants with T2DM alongside overweight/obesity while the remaining studies included overweight/obese subjects without a focus. Additional comorbidities of participants within the studies were not specifically outlined.

A detailed summary of key outcomes and quality ratings across each study can be found in Table 3. In addition, Table 3 also includes study design and sample size. The following results section explores the findings across the 12 studies with an emphasis on the outcomes of mean change in body weight, change in waist circumference, and adverse events.

3.1 Mean Change in Body Weight

The primary outcome of weight loss was measured through the mean change in body weight with various studies offering results both between and within study groups. Eleven studies reported higher mean changes in body weight in the intervention groups compared to placebo groups, strongly suggesting participants receiving GLP-1 treatment experienced significant weight losses across the majority of studies (Aroda et al., 2025; Buckeridge et al., 2022; Garvey et al., 2022; Golubic et al., 2024; Jastreboff et al., 2022; Ji et al., 2023; Pederson et al., 2021; Sanaa et al., 2024; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). The greatest mean change in weight between intervention groups versus a placebo group was observed in the study by Jastreboff et al., (2022), where the mean change in body weight for the 15 mg tirzepatide dosage group was -20.9% while the placebo group had a -3.1% change ($p<0.001$). Zhao and researchers (2024) also reported a substantial change in mean weight while trialing tirzepatide, where the 15 mg group had a -17.5% weight change versus a 2.3% weight change in the placebo group. Garvey and colleagues (2022) noted a -15.2% versus -2.6% weight change between a semaglutide intervention and a placebo ($p<0.0003$), while Wharton and their team (2024) found a -14.7% versus -2.3% weight change between the orforglipron group and a placebo. Lastly, the study by Ji et al., (2023) concluded a -11.3% versus a -1.0% weight change between a mazdutide group and a placebo. This similar trend in weight change between intervention and placebo can continue to be observed throughout the remainder of the aforementioned studies and strongly suggests a relationship between GLP-1 treatment and weight loss.

In addition to the widely observed differences in mean body weight changes between intervention and placebo groups, a strong association within intervention groups surrounding mean change in body weight was also shown. More specifically, intervention groups with higher dosages of GLP-1s had greater changes in mean body weight compared to groups administered lower dosages (Aroda et al., 2025; Buckeridge et al., 2022; Jastreboff et al., 2022; Ji et al., 2023; Pederson et al., 2021; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). Identically to the between study group measure, Jastreboff and associates (2022) had

the largest gap in mean body weight change among the intervention groups, with the lowest dosage group, 5 mg of tirzepatide having a -15% change while the highest dosage group, 15 mg of tirzepatide had a -20.9% change ($p<0.001$). Wharton et al., (2024) and Ji et al., (2023) both had the next greatest disparities, reporting a -7.1% versus a -12.3% change in mean body weight ($p<0.001$) and a -6.7% versus a -11.3% change in mean body weight, respectively, between the lowest and highest dosage groups. This pattern of greater dosage amounts leading to increased losses in weight persists among the remainder of the listed studies, although results not fully described. With the significant changes in body weight both between and within study groups, the research strongly indicates GLP-1 as an intervention is effective at reducing body weight when compared to a placebo, with more robust results at higher dosages.

3.2 Change in Waist Circumference

In conjunction with mean change in body weight, waist circumference acts as an additional indicator of overall health and visceral fat abundance. Among all the studies, four studies provided significant results surrounding participant changes in waist circumference (Garvey et al., 2022, Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). Throughout the studies, reductions in waist circumference were more widely observed in intervention groups as opposed to placebo groups. Zhao and colleagues (2024) displayed the greatest difference in waist circumference changes between the intervention and placebo groups, with a -14.5 cm change in the 15 mg tirzepatide group and only a -2.6 cm change in the placebo ($p<0.001$). Wharton and researchers (2024) showed a -13.6 cm participant waist circumference change while taking 45 mg of orforglipron versus a -4 cm waist circumference change for the placebo group. Garvey and team (2022) displayed similar results with a -14.4 cm waist circumference difference versus a -5.2 cm change ($p<0.0001$) when measuring a semaglutide intervention against a placebo. While a concrete value was never mentioned for the placebo group in the study by Zhu et al., (2024), the change in waist circumference was communicated as the change from the placebo, this value being -3.9 cm circumference change in the 1.2 mg group trialing ecnoglutide ($p<0.0001$). Correspondingly to the changes in mean body weight, decreases in waist circumference were also observed as GLP-1 dosage increased. Overall, studies discussed thus far have provided significant findings supporting the use of GLP-1 intervention for the purpose of weight loss and decreasing waist circumference.

3.3 Adverse Events

Characteristic of all drug trials, side effects can occur and are often observed and recorded by participants throughout the duration of the intervention period. Of the 12 studies, eight included participants who reported adverse events in relatively high percentages, ranging from mild to moderate intensities (Aroda et al., 2025; Aronne et al., 2025; Buckeridge et al., 2022; Garvey et al., 2022; Jastreboff et al., 2022; Ji et al., 2023; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). The study performed by Zhao and researchers (2024) contained the largest proportion of self-reported adverse events, with 95.7% of participants in the 10 mg tirzepatide group and 82.6% in the placebo. The second highest percentage of adverse events were reported by participants in the Ji et al. (2023) study, with 95.2% and the placebo group clocking in at 80.6%. The remainder of the studies reported adverse event occurrences ranging from 76% to 90%. As for events considered more on the severe side (events considered more debilitating or life-threatening), three studies had this inclusion as a reported outcome (Aronne et al., 2025; Garvey et al., 2022; Zhao et al., 2024). Four percent of participants reported severe adverse events in the study by Aronne et al., (2025), while Zhao

and colleagues (2024) found 7.8% of the tirzepatide group and 1.4% of the placebo group reported severe events. Lastly, Garvey and team (2022) had the highest incidence of reported severe adverse events with 7.9% from the semaglutide group and 11.8% from the placebo group. Given the high rates of reported mild to moderate adverse events, values strongly support the association between the usage of GLP-1 medication and side effects, most commonly consistent with GI discomfort. Conclusions surrounding severe-level events remain uncertain as such events are undefined and low in number.

3.4 Risk of Bias and Quality Assessment

The Quality Criteria Checklist (QCC) from the Academy of Nutrition and Dietetics was used to assess the quality of the literature and risk of bias (Academy of Nutrition and Dietetics, 2022). Table 3 includes the grades for each study with each receiving a rating of positive (+), neutral (Ø), or negative (-) based on relevance and validity. Additionally, a grade (I-V) was assigned in accordance with the strength of evidence presented. Out of the studies, one received a positive rating, indicating the authors proficiently addressed any problems concerning inclusion/exclusion, biases, generalizability, and collection of data. Six received a neutral rating, indicating studies were neither strong nor weak in these regards. The remaining five studies received a negative rating, indicating problems mentioned within the positive rating were not adequately addressed. For instance, a study containing major biases without any clarification behind them. As for grades, only one study was graded I, six were graded II, and five were graded III. The study with grade I had strong study designs, consistent findings, large sample sizes, high clinical impact, and were without doubts about generalizability. Studies assigned grades II and III had weaker versions of those elements, such as small sample sizes or non-controlled trials. Overall, the majority of studies held neutral quality and evidence strength within the review.

Table 3. Article Summary Table

Reference	Population	Intervention	Results	Conclusions	Quality Grade
Aroda et al (2025)	-Initial (n=245) (125 males, 120 females) -Semaglutide 2 mg (n=61), 8 mg (n=62), 16 mg (n=62), placebo (n=60) -Final (n=219)	-Dosages at 0.29 mg once weekly and increased until target dose was reached -40 weeks	- <u>Mean % body weight change</u> : 2 mg = -7.3%, 8 mg = -8.3%, 16 mg = -10.8%, placebo = -2% - <u>AEs</u> : 2 mg = 72%, 8 mg = 90%, 16 mg = 89%, placebo = 63%	Higher doses of semaglutide provide greater weight losses in comparison to lower doses in individuals with T2DM and overweight or obesity	(+) Grade II
Aronne et al (2025)	-Initial (n=750) (265 males, 485 females) -Tirzepatide (n=374) & semaglutide (n=376) -Final (n=637)	-Both tirzepatide and semaglutide dosages increased over time until target was met -Nutrition and physical activity counseling -72 weeks	- <u>LS mean % change in body weight</u> : tirzepatide = -20.2% vs semaglutide = -13.7% (p<0.001) - <u>LS mean change in waist circumference</u> : tirzepatide = -18.4 cm vs semaglutide = -13.0 cm (p<0.001) - <u>AEs</u> : tirzepatide = 76.7% vs semaglutide = 79% - <u>Severe AEs</u> : 4%	Both drugs resulted in significant body weight & waist circumference reductions with tirzepatide showing superior outcomes	(Ø) Grade II

Reference	Population	Intervention	Results	Conclusions	Quality Grade
Buckner et al (2024)	-Initial (n=66) (35 males, 31 females) -T2DM 28-day (n=40), T2DM 42-day (n=11), obesity 42-day (n=15) -Final (n=61)	-Lotiglipron once daily and increased over time until target dosage reached -28 or 42 days	- <u>Body weight reductions</u> : T2DM 120 mg = -4.66 kg, T2DM 180 mg = -5.10 kg, T2DM placebo = -2.65 kg, obesity = -4.97 kg, obesity placebo = -3.43 - <u>AEs</u> : greater in higher lotiglipron dosage groups	Lotiglipron in obese adults with or without T2DM reduces body weight with safety and tolerability profiles similar to other GLP-1s	(-) Grade III
Garvey et al (2022)	-Initial (n=304) (68 males, 236 females) -Semaglutide 2.4 mg (n=152) & placebo (n=152) -Final (n=282)	-Semaglutide initiated at 0.25 mg, increased over time until maintenance dose of 2.4 mg was reached -Participant behavioral counseling -104 weeks	- <u>Mean change in body weight</u> : semaglutide = -15.2% vs placebo = -2.6% (p<0.0001) - <u>Waist circumference reductions</u> : semaglutide = -14.4 cm vs placebo = -5.2 cm (p<0.0001) - <u>AEs</u> : semaglutide = 82.2% vs placebo = 53.9% - <u>Severe AEs</u> : semaglutide = 7.9% vs placebo = 11.8%	Semaglutide with behavioral counseling was associated with sustained weight loss in adults with overweight and obesity	(Ø) Grade II
Golubic et al (2024)	-Initial (n=28) (25 males, 3 females) -Cotadutide (n=19) & placebo (n=9) -Final: (n=19)	-Both treatments had a fixed dose escalation of 100 µg daily for first 4 days, then 200 µg for next 4 days, and 300 µg for the remaining 34 days -42 days	- <u>Weight loss</u> : cotadutide = 4% - <u>Between-group difference LS mean</u> : -2.6% (p=0.011) - <u>Total fat mass reduction</u> : cotadutide vs placebo (-3.3 kg vs -1.4 kg; p=0.085)	Cotadutide leads to significant weight loss predominantly via reduced energy intake in overweight and obese adults.	(-) Grade III
Jastreboff et al (2022)	-Initial (n=2,539) (825 males, 1,714 females) -Tirzepatide 5 mg (n=630), 10 mg (n=636), 15 mg (n=630), placebo (n=643) -Final (n=2,183)	-Tirzepatide initiated at 2.5 mg and increased by 2.5 mg every 4 weeks to reach maintenance dose -Lifestyle intervention counseling -72 weeks	- <u>Treatment estimand mean change in weight</u> : 5 mg = -15%, 10 mg = -19.5%, 15 mg = -20.9%, placebo = -3.1% (p<0.001 for all comparisons) - <u>AEs</u> : tirzepatide = 78.9% - 81.8% vs placebo = 72%	Tirzepatide at varying doses administered once weekly demonstrated substantial weight reduction in obese adults	(Ø) Grade I
Ji et al (2023)	-Initial (n=248)	-Mazdutide and placebo were	- <u>Mean % change in body weight</u> : 3 mg =	In overweight and obese adults,	(-) Grade

Reference	Population	Intervention	Results	Conclusions	Quality Grade
	(119 males, 129 females) -Mazdutide 3 mg (n=62), 4.5 mg (n=63), 6 mg (n=61), placebo (n=62) -Final (n=224)	taken once weekly subcutaneously with increasing dose levels -24 weeks	-6.7%, 4.5 mg = -10.4%, 6 mg = -11.3%, placebo = 1.0% - <u>AEs</u> : all treatment groups = 95.2% vs placebo = 80.6%	mazdutide led to clinically meaningful and significant reductions in body weight	III
Pederson et al (2021)	-Initial (n=1,210) -Semaglutide 1 mg (n=403), 2.4 mg (n=404), placebo (n=403) -Final (n=1,131)	-Once weekly semaglutide 1 mg, 2.4 mg, and a placebo -68 weeks	- <u>Mean weight loss</u> : 1 mg = 7%, 2.4 mg = 9.6%, placebo = 3.4% (p<0.0001)	Higher doses of semaglutide lead to increased weight losses in adults with T2DM and overweight or obesity	(-) Grade III
Sannaa et al (2024)	-Initial (n=136) (18 males, 118 females) -Liraglutide (n=67) vs placebo (n=69) -Final (n=124)	-Liraglutide dosage increased by 0.6 mg daily for one week and by 0.6 mg weekly until 3 mg was reached -Behavioral counseling for weight reduction -16 weeks	-Weight loss of >4 kg for liraglutide compared to placebo OR=12.9 (p<0.0001)	Liraglutide treatment leads to effective weight loss associated with gastric emptying retardation and caloric consumption	(-) Grade III
Wharton et al (2024)	-Initial (n=272) (111 males, 161 females) -Orforglipron 12 mg (n=50), 24 mg (n=53), 36 mg (n=58), 45 mg (n=61), placebo (n=50) -Final (n=235 completed trial)(n=207 completed treatment)	-There was a dose escalation phase that lasted up to 16 weeks and the dosages were cohort-dependent -Healthy eating and exercise education -36 weeks	- <u>Mean % change in body weight</u> : -9.4% to -14.7% in a dose dependent manner vs placebo -2.3% - <u>Mean % change in body weight</u> for all doses of orforglipron from -7.1% to -12.3% (p<0.001) - <u>Waist circumference reductions</u> : 12 mg = -9.6 cm, 24 mg = -11.2 cm, 36 mg = -10.6 cm, 45 mg = -13.6 cm, placebo = -4 cm - <u>AEs</u> : orforglipron = 90% vs placebo = 76%	Orforglipron is associated with weight reduction and similar benefits in overweight and obese adults comparably to other injectable GLP-1 agonists.	(Ø) Grade II
Zhao et al (2024)	-Initial (n=210) (107 males,	-Tirzepatide dosage began at 2.5 mg and increased by 2.5	- <u>Mean % change in body weight</u> : 10 mg = -13.6%, 15 mg = -17.5%, placebo = -2.3%	Tirzepatide administered in both 10 mg and 15 mg dosages	(Ø) Grade II

Reference	Population	Intervention	Results	Conclusions	Quality Grade
	103 females) -Tirzepatide 10 mg (n=70), 15 mg (n=71), placebo (n=69) -Final (n=201 completed study) (n=182 completed treatment)	mg every 4 weeks until target dosage was reached -Lifestyle intervention -52 weeks	- <u>Waist circumference reduction</u> : 10 mg = -11.4 cm, 15 mg = -14.5 cm, placebo = -2.6 cm in placebo (p<0.001 for both treatment groups) - <u>AEs</u> : 10 mg = 95.7%, 15 mg = 90.1%, placebo = 82.6% - <u>Severe AEs</u> : both treatment groups = 7.8% vs placebo = 1.4%	resulted in a significant weight reduction compared to a placebo	
Zhu et al (2024)	-Initial (n=145) (93 males, 52 females) -Ecnoglutide 0.4 mg (n=37), 0.8 mg (n=36), 1.2 mg (n=36), placebo (n=36) -Final (n=140)	-Ecnoglutide dosages began at 0.2/0.3 mg with fixed double dose increments until the target dose was reached for each respective group -20 weeks	- <u>LS mean body weight change</u> : 0.4 mg = -1.57 kg, 0.8 mg = -1.65 kg, 1.2 mg = -2.26 kg, placebo = 0.5 kg (p<0.0001) - <u>Waist circumference reduction from placebo</u> : 0.4 mg = -1.3 cm, 0.8 mg = -1.16 cm, 1.2 mg = -3.9 cm (p<0.0001) - <u>Adverse AEs</u> : all treatments groups = 72.2-78.4%	Ecnoglutide is a beneficial treatment for body weight reduction with a safety profile consistent and comparable to other GLP-1 based therapies	(Ø) Grade II

4. Discussion

The effects on body weight, waist circumference, and incidence of adverse events among each study population were shown to be relatively homogenous throughout this review. Although the type of GLP-1 interventions varied from study to study, overall mechanisms and end-outcomes remained similar. With barely any data in opposition, the results of this review should be of potential notability.

4.1 Mean Change in Body Weight

Throughout the studies included in this review, the efficacy and effectiveness of GLP-1s remained consistent despite the numerous variations of the drug being tested. Very few, if any, of the studies had clashing results, but were rather in agreement with one another. The primarily favored outcome was the mean change in body weight when compared to a placebo, with substantial reductions observed throughout many of the studies (Aroda et al., 2025; Buckeridge et al., 2022; Garvey et al., 2022; Golubic et al., 2024; Jastreboff et al., 2022; Ji et al., 2023; Pederson et al., 2021; Sanaa et al., 2024; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). While Aronne and their team (2025) did not include a placebo group in their study, the least-squares (LS) mean % change in body weights still showed statistical significance (p<0.001). This same body weight trend was upheld among the remaining populations even with slight differences in gender, age, BMI, and presence of diabetes mellitus. For instance, Buckeridge and colleagues (2024) had wide participant inclusivity, their study enrolling adults with overweight, obesity, T2DM, BMIs <24.5 kg/m², and both males and females, with each intervention group showing robust decreases in body weight. The overall uniformity in body weight outcomes stands as a strong proponent for GLP-1s in the treatment of weight loss.

4.2 Within-Group Dosage Efficacy and Escalation

While 11 of the 12 studies implemented a placebo to act as a baseline for the intervention, the measured efficacies between the intervention groups themselves are notable. To clarify, most studies involved multiple intervention groups receiving either the same or different GLP-1s at different dosage amounts (e.g. 2 mg tirzepatide, 4 mg tirzepatide, and a placebo dosage). Moreover, many studies utilized a dose escalation phase within their treatment periods. This phase involved participants beginning the trial receiving a relatively low dosage of the drug with the dosage steadily increasing over time, usually in increments, until a target/end dosage is achieved. The element of multiple dosage groups not only strengthens the quality of findings but also provides the ability to assess whether higher dosages of a given drug lead to greater results. Aroda and researchers (2025) had three separate semaglutide dosage groups of 2 mg, 8 mg, and 16 mg, with mean % body weight changes of -7.3%, -8.3%, and -10.8%, respectively. Likewise, Ji and their team (2022) trialed three mazdutide dosage groups of 3 mg, 4.5 mg, and 6 mg, once again recording mean % body weight changes of -6.7%, -10.4%, and -11.3% respectively. The aforementioned two research teams, alongside the other studies with multiple dosage groups, displayed an identical increase in efficacy as GLP-1 dosage amounts also rose, further supporting the relationship between higher dosages and increased efficacy.

4.3 Change in Waist Circumference

Under a similar measure to the mean change in body weight, findings drew a strong association between GLP-1 usage and depletions in waist circumference, which would be accompanied by additional benefits to overall health. The teams of Aronne et al., (2025), Garvey et al., (2022), Wharton et al., (2024), Zhao et al., (2024), and Zhu et al., (2024) focused on waist circumference as either a primary or secondary outcome. Each team found intervention groups with significant reductions in waist circumference in comparison to any placebo group. Zhao and researchers (2024) procured the largest difference between intervention and placebo groups with an 11.9 cm disparity in waist circumference. The other studies presented similarly high gaps except for Zhu and colleagues (2024), who reported a maximum reduction of 3.9 cm from the placebo, which most likely was attributed to the study's shorter treatment period of only 20 weeks, considerably less than their counterparts which ranged from 36 – 104 weeks. The covariation of both mean body weight and waist circumference throughout the studies suggests GLP-1 usage does not solely target lean body mass, but also intra-abdominal fat stores. This deduction would then indicate GLP-1s may also lower the health risks associated with high waist circumference (e.g. cardiovascular disease, diabetes mellitus, and hypercholesterolemia).

4.4 Additional Interventions

Acknowledging total observed reductions in body weight were not solely attributable to GLP-1 usage across every study is of major importance. Around half of the studies included utilization of some type of lifestyle/nutrition counseling for their participants (Aronne et al., 2025; Garvey et al., 2022; Jastreboff et al., 2022; Sanna et al., 2024; Wharton et al., 2024; Zhao et al., 2024). For example, Sanna and team (2024) offered behavioral counseling for weight reduction, Wharton and researchers (2024) provided healthy eating and exercise education, and Zhao and colleagues (2024) issued lifestyle interventions promoting adherence to healthy meals and consistent physical activity. Most sessions were led by Registered Dietitians or other allied health professionals. This additional type of intervention is important to note, as the inclusion may potentially affect how results from the studies are interpreted. When comparing the efficacies of GLP-1 drugs between studies, taking various types of auxiliary interventions into account may be beneficial.

4.5 Adverse Events

Adverse events, or side effects, can be relatively characteristic of GLP-1 usage. The most common types of adverse events across studies were mainly GI related: Nausea, vomiting, stomach pain, loss of appetite, diarrhea, and constipation (Aroda et al., 2025; Aronne et al., 2025; Garvey et al., 2022; Jastreboff et al., 2022; Ji et al., 2023; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). Many studies had participants from the intervention groups report on the incidence of any adverse events (Aroda et al., 2025; Aronne et al., 2025; Buckeridge et al., 2024; Garvey et al., 2022; Jastreboff et al., 2022; Ji et al., 2023; Wharton et al., 2024; Zhao et al., 2024; Zhu et al., 2024). The occurrence of adverse events varied from 72%-95.7% throughout the studies and ranged from mild to moderate in nature. More severe events did arise, although only recorded in three studies. The teams of Aronne et al., (2025), Garvey et al., (2022), and Zhao et al., (2024) each had a 4%, 7.9%, and 7.8% incidence of severe events among the intervention groups, respectively. Events under the 'severe' category varied far greater than those considered 'mild to moderate' as severe events mainly comprised of more debilitating and potentially life-threatening conditions. Conversely, the presence of any adverse events within the placebo groups is an intriguing topic. Unfortunately, no study included insight into why placebo group participants may have experienced any sort of discomfort. This phenomenon warrants further investigation for future research.

Due to only one study reporting high attrition rates (Aronne et al., 2025), combined with the somewhat low incidences of severe adverse events, the safety of GLP-1s could potentially be considered reasonable, although the high rates of mild to moderate adverse events should also not be ignored. While mild GI discomfort is generally accepted as tolerable, that would not stand true for every individual, since symptoms can be subjective. In terms of GLP-1s causing serious health problems, this does not appear to be a major concern according to the studies in this review.

4.6 In Relation to Professional Guidelines

The World Health Organization (WHO) recently addressed obesity as a continuous health challenge for individuals across the world. In response, the WHO released the organization's first guidelines surrounding the use of GLP-1s for the treatment of obesity. The WHO deemed obesity a serious problem and released conditional recommendations following the organization appending GLP-1 therapies to the Essential Medicines List for managing T2DM for high-risk groups back in September 2025. There are two primary conditional recommendations within the WHO guidelines: (1) GLP-1s may be used by adults for long-term treatment of obesity (excluding pregnant women); and (2) Interventions involving healthy nutrition behaviors and physical activity, coined 'intensive behavioral interventions', may be offered within a comprehensive multimodal algorithm. The WHO places additional emphasis on how GLP-1 medication will not solve the problem of obesity on its own. To properly address obesity, fundamental restructuring methods are warranted (World Health Organization, 2025). The WHO's guidelines for GLP-1 usage act as one of the first gateways towards globalizing the drug but do not come without stipulations.

The American Diabetes Association (ADA) has historically recommended GLP-1s as effective pharmacologic therapy for adults with T2DM. Guidelines for GLP-1s have often grouped them together alongside other therapies, such as SGLT-2 inhibitors and glucose-dependent insulinotropic peptides (GIP), in order to maximize glycemic management. In addition to T2DM, such combination therapies have also been recommended for adults

also impaired with heart failure, chronic kidney disease, and metabolic dysfunction-associated steatotic liver disease (American Diabetes Association Professional Practice Committee, 2024). Recently, the ADA has released guidance statements on GLP-1s as the clinical demand and popularity for them have dramatically increased over the last few years. As a form of weight loss therapy, the U.S. Food and Drug Administration (FDA) greenlit several incretin-based drugs (GLP-1s and DPP-4 inhibitors), which incidentally led to a demand exceeding the available supply. Consequently, multiple companies jumped to produce and market compounded formulations directly to buyers, with some consumers notably bypassing collaboration with their health care team before using the new drug. While these formulations are intended to meet consumer needs, the ADA has many concerns surrounding this widespread availability of these products, as they remain non-FDA-approved. The ADA advises against using non-FDA-approved compounded incretin products and recommends that consumers swapping to a different FDA-approved medication if one becomes unavailable. Once product unavailability subsides, the original FDA-approved medication should be reassessed for appropriate usage. With numerous key concerns regarding the quality, efficacy, and safety of newly manufactured incretin medications, the ADA generally recommends individuals with diabetes and/or obesity only use FDA-approved products (Neumiller et al., 2024).

While the Academy of Nutrition and Dietetics (AND) does not have concrete guidelines surrounding GLP-1 medications, the professional organization provided a brief statement addressing pharmaceutical manufacturers and obesity medications. The Academy has urged pharmaceutical companies and health care providers to enhance the success of obesity medications by referring patients to Registered Dietitians for medical nutrition therapy in conjunction with the GLP-1, or other weight loss medication, prescription. Access to lifestyle and nutritional interventions is imperative for properly addressing and managing obesity, a disease that is multifaceted. The Academy pushes for a comprehensive, collaborative and interprofessional approach (Academy of Nutrition and Dietetics, 2025).

The results of the studies in this review align with the recommendations and goals of the new WHO Guidelines. As shown by each study, GLP-1s are effective in reducing body weight and waist circumference in both overweight and obese individuals. Furthermore, the low rates of severe adverse effects potentially act as endorsement for the WHO's recommendation for long-term GLP-1 use. Although additional lifestyle/diet/exercise interventions weren't explored intensely for this review, their appearance in a few of the studies can only be alluded to their importance in conjunction with GLP-1 treatment, as advocated for by the Academy of Nutrition and Dietetics. With regard to the ADA's new guidelines concerning non-FDA-approved medications, the findings of this review do not directly disprove nor affirm what the ADA advises, as many of the studies are in the early clinical trial stages.

4.7 Risk of Bias and Quality Assessment

Many studies ($n = 6$) in this review received a neutral rating. This rating was awarded to studies performing average when addressing issues with inclusion/exclusion, generalizability, biases and data collection. For example, a few studies may have excelled at responding to identified biases but failed at responding to poor generalizability, leading to a net neutral rating. Other neutrally rated studies managed to just minimally address each issue evenly. The next largest grouping were five studies assigned a negative rating who underperformed in accounting for the aforementioned concerns, leaving many unanswered questions and gaps. There was only one study garnering a positive rating and excelling in overcoming most study design flaws. While this positively rated study was not without faults, it succeeded in

acknowledging them and providing bridges to any gaps. The grades for the studies followed the ratings identically, with six graded II, five graded III, and only one graded I. As a general guide, studies where the strengths outweighed the limitations tended to receive more positive ratings and higher grades, and vice versa. Conversely, the studies which equally weighed strengths and limitations were more likely to be rated neutrally and graded with a II. The dichotomy of the ratings and grades may be indicative of the strength, or weakness in a sense, of the evidence collected, although not reflective of the homogeneity of outcomes. Each study held similar findings, despite the differences in limitations. As a result, trends and general associations from the results could be drawn, but caution should be taken when making concrete statements.

4.8 Strengths

This review utilized the PRISMA Guidelines and Flowchart to identify and organize studies obtained via multiple databases as well as the Academy of Nutrition and Dietetics' Quality Criteria Checklist (QCC) to assess the quality of literature. Among the studies, multiple strengths were identified. Many studies were blinded, which reduced bias while others had high rates of adherence to treatment. Large sample sizes resulted in enhanced generalizability, low attrition rates aided in maintaining statistical power, and long treatment periods improved clinical relevance. Additionally, the evaluations of maximum GLP-1 dosages against fixed dosages provided deeper insight into drug efficacies. Lastly, the inclusion of any type of GLP-1 treatment helped increase the number of available studies.

4.9 Limitations

Several studies struggled with low diversity and a lack of generalizability in participants, along with short treatment periods, and small sample sizes. Fewer studies faced a lack of blinding, being indirectly affected by the COVID-19 pandemic, and a lack of accessibility to certain instruments and imaging techniques. With regards to the review itself, it was not fully comprehensive as it excluded numerous countries apart from the United States, the United Kingdom, Australia, and China, thus resulting in the inclusion of only 12 total studies. This geographic limitation may have exempted multiple populations and lowered external validity on the global scale. Moreover, the number of identified records initially collected was extremely high, leaving a possibility for mistakenly excluding eligible studies.

5. Applications for Practitioner

Research findings suggest the use of GLP-1s as a relatively safe and effective method for weight loss in overweight and obese individuals, with or without T2DM. If tolerated, elevated dosages of GLP-1s could potentially lead to greater reductions in weight but should be slowly increased over time until a target dosage is achieved, although a starting dosage and escalation amounts should be individualized from patient to patient dependent on tolerance and symptoms. Caution is advised as adverse events, ranging from mild to moderate and GI-related in nature, are common and will need to be known by the patient before undergoing treatment. There remains a small possibility for more severe adverse events to take place as well. If a patient wishes to maximize outcomes in body weight reduction, nutritional and lifestyle counseling may serve as additional interventions. Overall, further research surrounding alternative outcomes, comorbidities, and diverse populations is still needed as gaps remain in these specific areas.

6. Conclusion

GLP-1 receptor agonists and other variations can lead to significant reductions in body

weight when compared to a placebo in adults with overweight and obesity. Higher dosages of GLP-1s were directly proportional to increased body weight loss as well. Individuals with T2DM have historically been the target population for GLP-1s and this review was also able to further reinforce this application. Lastly, certain GLP-1s are comparable to and consistent with other GLP-1-based therapies when it comes to weight reduction and other health benefits associated with treating obesity/T2DM. However, the overall verdict concerning the safety of GLP-1s remains limited due to the heterogeneity in participant reporting of various adverse events. Future research will provide stronger evidence and conclusions as the use of GLP-1s for overweight and obese populations continues to gain popularity.

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Authors' contributions

GV and KH were responsible for the study design and revising. GV was responsible for data collection and drafted the manuscript, and KH provided revisions for multiple drafts. All authors read and approved the final manuscript

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