

## REVIEW OPEN ACCESS

# Low Weight Loss Response to Incretin Analogs: A Systematic Review

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## ABSTRACT

The development of GLP-1 and GIP analogs has been a significant breakthrough in type 2 diabetes and obesity pharmacotherapy. However, individual responses to these medications can vary widely. This systematic review examines factors associated with low or no weight loss response to GLP-1 and GIP analogs. Key predictors of poor response include higher baseline body weight, BMI, HbA1c, and insulin resistance. Genetic factors, such as variants in the GLP1R gene, may also influence treatment outcomes. Metabolic health status, particularly glycemic control and insulin sensitivity, plays a crucial role in determining weight loss efficacy. Adherence to medication regimens is strongly associated with treatment success, with each additional month of treatment linked to greater weight loss. Lifestyle factors, including dietary habits and physical activity, can modulate responses to these medications. Emerging evidence suggests that gut microbiome composition may mediate weight loss outcomes. Demographic factors such as male sex and older age are associated with lower weight loss responses. Understanding these predictors is essential for optimizing treatment strategies, setting realistic expectations, and moving towards a precision medicine approach in obesity care. Further research is needed to validate these findings in diverse populations and develop practical tools for clinical decision-making.

## 1 | Introduction

The global obesity epidemic continues to be a major public health challenge, with several million adults worldwide currently living with obesity [1]. Traditional treatments, such as lifestyle modification and bariatric surgery, have limitations in terms of long-term efficacy, accessibility, and patient acceptability [2].

In this context, the development of GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulintropic polypeptide) analogs has been a major breakthrough in obesity pharmacotherapy [3]. There has also been an appreciable response over the last few years to these medications indicated for weight loss,

although originally designed to target type two diabetes [3]. The amount of weight loss expected upon use of these drugs has increased with new analogs of the hormones [4].

These medications work by mimicking the effects of endogenous incretin hormones, which are released from the gut in response to food intake [3]. GLP-1 and GIP act on multiple targets in the body, including the brain, pancreas, and gastrointestinal tract, to promote satiety, slow gastric emptying, and improve glucose homeostasis. In clinical trials, GLP-1 analogs like liraglutide, semaglutide, and tirzepatide have demonstrated impressive weight loss efficacy, with average reductions of 10–15% of initial body weight [4–6].

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Tirzepatide, the most recently approved drug in this area, is a dual (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist. It is designed to enhance insulin secretion, suppress glucagon release, and slow gastric emptying, which collectively contribute to its effects on weight reduction and glycemic control [7–9].

However, as with any pharmacological interventions, individual responses to GLP-1 and GIP analogs can vary widely. While many patients achieve clinically meaningful weight loss, a subset of individuals shows minimal or no response [10]. This heterogeneity in treatment outcomes poses a challenge for clinicians and patients alike, as it can lead to frustration, non-adherence, and suboptimal resource utilization [11].

Understanding the factors that predict poor response to GLP-1 and GIP analogs is therefore crucial for optimizing treatment outcomes and moving towards a precision medicine approach in obesity care. By identifying individuals who are less likely to respond well to these medications, clinicians can tailor their treatment strategies, consider alternative or adjunctive therapies, and set realistic expectations with patients [2]. As the landscape of obesity pharmacotherapy continues to evolve, with new drugs and drug classes on the horizon, understanding the predictors of response will be key to maximizing the impact of these interventions on individual and population health. Here, we review the evidence regarding low or no weight loss response to GIP and GLP1 analogs and their implications for personalized management.

## 2 | Methods

In this study, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 statement) guidelines outlined by Page et al. [12]. We searched the following databases: PubMed, Medline, Cochrane Library, Web of Science, and Google Scholar. We conducted a Boolean search using “AND” and “OR” as operators in addition to parentheses and asterisks. Our subject retrieval words were the following: approved incretin analogs, GLP-1, GIP, weight loss, insulin resistance, diabetes, and obesity. The search did not involve the use of filters or year limits. We included randomized controlled trials with a placebo-controlled design, reviews, cohort studies, and retrospective studies.

Two reviewers worked together to select papers for inclusion and came to a consensus if there was disagreement on any paper. Inclusion criteria were as follows: Studies that included patients with overweight or obesity among adults. Exclusion criteria were as follows: Book chapters, abstracts, duplicated articles, and papers where the full text was not available.

Studies that met the criteria for inclusion were grouped under the following headings: Authors, journal, year of publication, title, study design, quality of evidence, main aim, findings, and % non-responders.

The methodological quality of the included studies was critically appraised. We also included recent systematic reviews, such as the one by Mariam et al. 2024 [13], to provide a comprehensive

overview of the current evidence on GLP-1 receptor agonists and dual GIP and GLP-1 receptor agonists for obesity management. Additionally, we considered relevant randomized controlled trials like the one by Garvey et al. [14] on liraglutide and Wilding et al. on semaglutide to assess the safety and efficacy of these incretin analogs in individuals with overweight or obesity [10].

## 3 | Results

The online data search resulted in 40 articles. Taking inclusion and exclusion criteria into account, 29 studies were included (Figure 1).

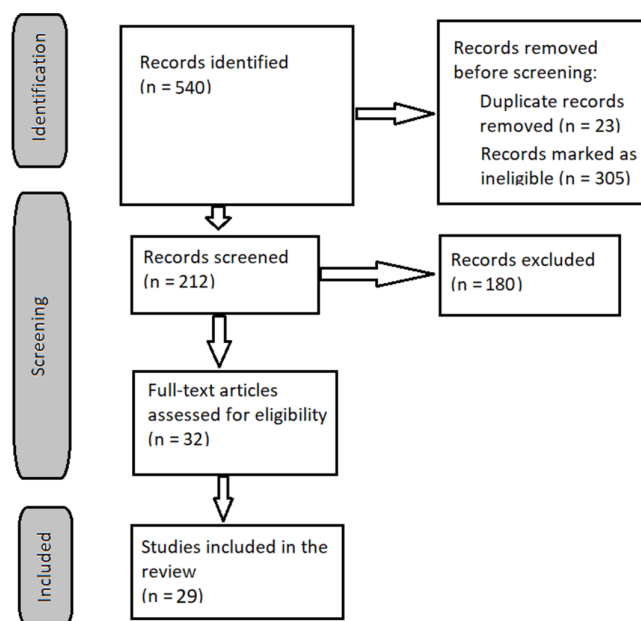
### 3.1 | Recent Clinical Studies

#### 3.1.1 | Trials—Liraglutide

The studies on liraglutide are mostly part of the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in individuals with and without diabetes) program, which includes trials like “SCALE Obesity and Prediabetes” and others focusing on weight management and diabetes risk reduction [5, 15].

**3.1.1.1 | Diabetes—Liraglutide.** Liraglutide primarily targets improvement in blood sugar among patients with type 2 diabetes. It is a glucagon-like peptide-1 (GLP-1) receptor agonist; it mimics the actions of GLP-1, a hormone that plays a role in regulating blood sugar and appetite. It stimulates the pancreas to release more insulin when blood sugar levels are high, helping to lower them. It also reduces glucagon secretion, another hormone that raises blood sugar levels [15].

**3.1.1.2 | Obesity—Liraglutide.** Liraglutide leads to a feeling of fullness that potentially aids weight loss, which is useful



**FIGURE 1** | PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) algorithm showing the articles selected for the systematic review.

for weight management. Its mechanism of action enhances insulin secretion, inhibits glucagon release, and slows gastric emptying, which collectively contributes to reduced appetite and weight loss [5, 16].

Based on clinical trial data, the weight loss plateau with liraglutide typically follows this pattern: Initial weight loss begins within the first 4–8 weeks; significant weight loss occurs within the first 16 weeks, with continued effects up to 56 weeks. The average weight loss at plateau is approximately 5–8% of initial body weight, with some individuals experiencing greater losses [5, 16]. In the long term, over a 3-year period, liraglutide continued to support weight management, although the initial rapid weight loss slowed down [15].

### 3.1.2 | Trials—Semaglutide

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist that has been shown to be effective in managing weight and improving glycemic control in individuals with type 2 diabetes. The **Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trial** program comprises 6 phase 3a trials (SUSTAIN 1 through 6) along with 2 phase 3a trials. The Semaglutide Treatment Effect in People with obesity (STEP) clinical trial program evaluated once-weekly subcutaneous semaglutide 2.4 mg in people with overweight or obesity.

**3.1.2.1 | Diabetes—Semaglutide.** The SUSTAIN trials compared semaglutide with placebo (as **monotherapy** or add-on to basal insulin) or with the antihyperglycemic agents **sitagliptin**, **exenatide extended-release**, and **insulin glargine**. The SUSTAIN 6 phase 3a trials investigated the safety, efficacy, and long-term cardiovascular (CV) outcomes with semaglutide vs. placebo in adults with type 2 diabetes at high risk for CV events. The phase 3b SUSTAIN 7 trial was a head-to-head comparison of semaglutide vs. **dulaglutide** [17]. It is established that semaglutide injection, used along with a diet and exercise program, can control blood sugar levels in adults. Semaglutide injection is used to treat type 2 diabetes. This medicine is also used to lower the risk of heart attack, stroke, or death in patients with type 2 diabetes, obesity, and heart or blood vessel disease.

**3.1.2.2 | Obesity—Semaglutide.** The STEP program has provided valuable insights into the predictors of weight loss response to semaglutide. Across STEP 1, 3, 4, and 8, semaglutide 2.4 mg was associated with mean weight losses of 14.9%–17.4% in individuals with overweight or obesity without type 2 diabetes from baseline to week 68.

The STEP 2 trial demonstrated that semaglutide 2.4 mg once weekly resulted in a mean weight loss of 9.6% compared with 3.4% with placebo over 68 weeks, highlighting its superior efficacy in weight reduction among patients with type 2 diabetes and obesity [18–20]. Additionally, semaglutide significantly improved cardiometabolic parameters, which are crucial for reducing the risk of diabetes-related complications [20, 21].

The STEP 1 trial [4] was a 68-week, randomized, double-blind, placebo-controlled study of once-weekly subcutaneous

semaglutide 2.4 mg in 1961 adults with obesity or overweight. The study found that participants treated with semaglutide achieved a mean weight loss of 14.9% (95% CI, 13.8 to 16.0) compared with 2.4% (95% CI, 1.3 to 3.5) with placebo.

The STEP 4 trial investigated whether early weight loss could predict long-term weight loss outcomes with semaglutide. Nine hundred and two (902) participants initiated semaglutide at week 0, of whom 803 were randomized at week 20 (semaglutide:  $n = 535$ , placebo:  $n = 268$ ; characteristics at week 0 for all randomized participants: mean age 46 years, body weight 107.2 kg, BMI 38.4 kg/m<sup>2</sup>; 79.0% female; 83.7% white). The study found that early responders (those who lost  $\geq 5\%$  body weight by week 20) were more likely to achieve clinically relevant weight loss by week 68.

For the 88.0% of participants randomized to semaglutide and who were responders at week 20, the mean body weight change from week 0 to 68 was  $-19.7\%$ . For non-responders at week 20, mean body weight change was  $-6.4\%$  with continued semaglutide vs.  $-0.3\%$  with switch to placebo. Of all participants randomized to semaglutide, 86.2% achieved a clinically relevant weight loss ( $\geq 5\%$ ) at week 68. Being a responder at week 20 was highly predictive of achieving this outcome (positive predictive value: 96.4%), whereas being a non-responder at week 20 had limited predictive value (negative predictive value: 42.9%). Although the authors found that the effect of early weight loss had little impact on the achievement of at least 5% weight loss by the end of the trial. Nevertheless, overall weight loss with semaglutide was greater among early responders, but non-responders also achieved a clinically relevant weight loss. The findings underscore the possible importance of early response as a predictor of long-term success with semaglutide treatment.

The STEP 2 trial, which is part of the clinical trial program, provides insights into the time to weight plateau. Participants in the trial experienced significant weight loss, with the most substantial reductions occurring within the first 68 weeks of treatment. However, the data suggests that weight loss may plateau after this period, as observed in other STEP trials where weight loss was maintained but did not significantly increase beyond the initial period [18–20].

### 3.1.3 | Trials—Tirzepatide

The SURMOUNT (the trial acronym for tirzepatide in weight loss trials) and SURPASS (trial acronym for tirzepatide in diabetes trials) have provided extensive data on its efficacy, safety, and potential predictors of response, contributing to a better understanding of its role in managing obesity and type 2 diabetes.

**3.1.3.1 | Diabetes—Tirzepatide.** The SURPASS trials 1–5 assessed the efficacy of tirzepatide in glycemic control and weight loss in adults with type 2 diabetes. The authors aimed to assess the efficacy, safety, and tolerability of the novel dual GIP and GLP-1 receptor agonist tirzepatide. Given as a once-weekly medication for the treatment of type 2 diabetes, it demonstrated statistically significant glycated hemoglobin (A1C) and weight reductions versus semaglutide [6, 22].

Each SURPASS trial was designed to provide insights into tirzepatide's potential as a treatment for type 2 diabetes. SURPASS-1 evaluated the efficacy and safety of three tirzepatide doses (5 mg, 10 mg, and 15 mg) as monotherapy against placebo among people with type 2 diabetes [22]. SURPASS-2 and SURPASS-3 [23] compared the efficacy and safety of the same three doses of tirzepatide to injectable semaglutide 1 mg and insulin degludec, respectively. SURPASS-5 evaluated the efficacy and safety of tirzepatide as an add-on to insulin glargine compared with placebo.

More participants on tirzepatide than on placebo met HbA1c targets of less than 7.0% ( $< 53$  mmol/mol; 87%–92% vs. 20%) and 6.5% or less ( $\leq 48$  mmol/mol; 81%–86% vs. 10%) and 31%–52% of patients on tirzepatide versus 1% on placebo reached an HbA1c of less than 5.7% ( $< 39$  mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from 7.0 to 9.5 kg [24].

**3.1.3.2 | Obesity—Tirzepatide.** The SURMOUNT trials examined the effects of tirzepatide on blood pressure and weight reduction in people with obesity [25–27]. Tirzepatide has shown promising results in weight reduction and glycemic control across various trials, with its dual mechanism of action targeting both GIP and GLP-1 receptors.

In the SURMOUNT-1 trial, tirzepatide treatment led to significant weight reduction, with the most substantial changes observed within the first 24 weeks. The weight loss effects tended to stabilize thereafter, maintaining a plateau until the end of the 72-week observation period [26, 27].

SURMOUNT 4 was conducted to assess the effect of tirzepatide on the maintenance of body weight reduction among individuals with obesity or overweight. The authors found that withdrawal of tirzepatide led to substantial weight gain after treatment was discontinued [28].

### 3.2 | Genetic Factors

Emerging evidence suggests that genetic factors may influence individual responses to GLP-1 and GIP analogs [29, 30]. In a cohort of 57 women with polycystic ovary syndrome (PCOS) treated with liraglutide 1.2 mg daily for 12 weeks, the participants were classified as strong responders if they lost  $\geq 5\%$  of initial weight. The authors found that carriers of at least one polymorphic rs10305420 allele had poor treatment outcomes compared with carriers of at least two wild-type C alleles. Odds ratio (OR)=0.27, 95% confidence interval (CI)=0.09–0.85,  $p$ -value=0.025 [31]. In addition, carriers of the allele had approximately 73% lower odds of achieving significant weight loss. This genetic association remains significant after controlling for baseline weight in multivariate regression (OR=0.26, 95% CI=0.08–0.84,  $p=0.024$ ) [24].

Mosenzon et al. [32] conducted a genome-wide association study (GWAS) to identify genetic determinants of weight loss response to semaglutide in 2808 participants from the STEP 1 trial. The authors found that rs10305420, a common variant in the GLP1R gene, was associated with a 1.3 kg lesser weight loss per allele (95% CI, 0.6 to 2.0;  $p=1.9 \times 10^{-4}$ ).

### 3.3 | Baseline BMI and Body Composition

Baseline BMI and body composition have consistently emerged as important predictors of weight loss response to GLP-1 and GIP analogs across multiple clinical trials. In the STEP 1–5 trials, which evaluated the efficacy and safety of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, higher baseline BMI was associated with greater absolute weight loss but lower percentage weight loss [4, 18, 33–35]. In addition to BMI, baseline body composition may influence weight loss response to GLP-1 and GIP analogs. Dual-energy X-ray absorptiometry (DEXA) was used to assess changes in body composition in a sub-study of the STEP 1 trial. Among 140 participants with available DEXA data, those with higher baseline lean mass experienced smaller reductions in scale weight but greater improvements in body fat percentage. These changes are observed early in the treatment and are sustained over time, highlighting the efficacy of semaglutide in improving body composition while preserving muscle mass [10]. In addition, administration of semaglutide with the inclusion of intensive behavioral therapy and initial low-calorie diet led to significantly greater weight loss. However, the sustainability of use of this drug under these circumstances is yet to be determined [33, 34].

### 3.4 | Metabolic Health Status

Metabolic health parameters, such as glycemic control and insulin resistance, have been shown to influence weight loss response to GLP-1 and GIP analogs. Pratley et al. [36] conducted a post hoc analysis of the SUSTAIN 7 trial, which compared the efficacy and safety of semaglutide versus dulaglutide in adults with type 2 diabetes. Among 1201 participants, those with higher baseline HbA1c and fasting plasma glucose experienced significantly smaller reductions in body weight at 40 weeks. For example, participants with a baseline HbA1c  $\leq 7.5\%$  lost an average of 5.4 kg with semaglutide 1.0 mg, compared with 3.8 kg for those with a baseline HbA1c  $> 8.5\%$  ( $p=0.02$  for interaction). Similarly, participants with a baseline fasting plasma glucose  $\leq 8.9$  mmol/L lost an average of 5.3 kg, compared with 3.9 kg for those with a baseline fasting plasma glucose  $> 11.0$  mmol/L ( $p=0.03$  for interaction). In addition, the STEP 2 trial [18] focused on the efficacy and safety of semaglutide 2.4 mg once weekly in 1210 adults with overweight or obesity and type 2 diabetes. At 68 weeks, the mean change in body weight was  $-9.6\%$  (95% CI,  $-10.4$  to  $-8.8$ ) with semaglutide versus  $-3.4\%$  (95% CI,  $-4.2$  to  $-2.6$ ) with placebo. Notably, the study found that baseline HbA1c was inversely associated with weight loss magnitude. For participants with a baseline HbA1c  $\leq 8\%$ , the mean weight loss was 11.2%, compared with 7.1% for those with a baseline HbA1c  $> 9\%$ .

In SURPASS-1, all three tirzepatide doses demonstrated statistically significant and clinically meaningful improvements in HbA1c and body weight reductions compared with placebo. Up to 92% of participants on tirzepatide achieved an HbA1c of less than 7%, which is the ADA's recommended target for most people with diabetes. Up to 52% achieved an HbA1c of less than 5.7%—the level for people without diabetes.

In SURPASS-2, all three tirzepatide doses delivered superior HbA1c and body weight reductions from baseline compared

with semaglutide. Up to 92% of participants on tirzepatide achieved an HbA1c of less than 7%, and up to 51% achieved an HbA1c of less than 5.7% [37].

In SURPASS-5, all three tirzepatide doses delivered superior HbA1c reductions and weight reductions compared with placebo, both added to titrated insulin glargine. Up to 97% of participants on tirzepatide achieved an HbA1c of less than 7%, and up to 62% of participants on tirzepatide achieved an HbA1c of less than 5.7% [23].

Insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR), has also been identified as a predictor of weight loss response to GLP-1 and GIP analogs. Matikainen et al. 2014 found that GLP-1 responses are heritable and blunted in acquired obesity with high liver fat and insulin resistance [38].

### 3.5 | Adherence to Medication Regimen

Weiss et al. conducted a retrospective cohort study using United States claims data to evaluate the impact of medication adherence on weight loss outcomes with GLP-1 receptor agonists. Among 14,194 adults with obesity who initiated liraglutide or semaglutide, those with high adherence (proportion of days covered  $\geq 80\%$ ) achieved significantly greater weight loss at 6 months compared with those with low adherence (proportion of days covered  $< 50\%$ ). After adjusting for baseline characteristics, high adherence was associated with a 2.1 percentage point greater weight loss (95% CI, 1.7 to 2.5) compared with low adherence [39]. Further, Lingvay et al. 2022 [40] discussed real-world evidence on the importance of medication adherence for weight loss outcomes with semaglutide. In this retrospective cohort study of 23,687 adults initiating semaglutide in the United States, the authors found a strong dose-response relationship between treatment duration and weight loss. Participants who persisted with treatment for  $\geq 6$  months achieved a mean weight loss of 7.1%, compared with 4.1% for those who discontinued within 3 months. After adjusting for baseline characteristics, each additional month of treatment was associated with a 0.6 percentage point greater weight loss (95% CI, 0.5 to 0.7).

### 3.6 | Dietary Habits and Physical Activity

Lifestyle factors, such as dietary habits and physical activity, can modulate weight loss responses to GLP-1 and GIP analogs. Wilding et al. investigated the interaction between semaglutide treatment and dietary energy density in a secondary analysis of the STEP 1 trial. Among 1961 participants, those who reduced their dietary energy density (kcal/g) in response to semaglutide achieved significantly greater weight loss at 68 weeks compared with those who maintained or increased their energy density. For each 1 kcal/g reduction in energy density, the expected weight loss increased by 1.7 kg (95% CI, 1.0 to 2.4) in the semaglutide group. These findings suggest that the appetite-suppressing effects of semaglutide may facilitate changes in dietary habits that enhance weight loss outcomes [4].

Physical activity may also potentiate the weight loss effects of GLP-1 and GIP analogs. Rubino et al. [35] conducted a randomized trial comparing semaglutide 2.4 mg once weekly with or without a structured exercise program in 200 adults with overweight or obesity. At 68 weeks, participants in the semaglutide plus exercise group achieved a mean weight loss of 17.1%, compared with 13.5% in the semaglutide alone group ( $p = 0.02$ ).

### 3.7 | Gut Microbiome Composition

The gut microbiome has emerged as a potential mediator of weight loss response to GLP-1 and GIP analogs [41]. Shang et al. found that liraglutide treatment is associated with baseline HbA1c, blood urea nitrogen, and gut microbiota composition in type 2 diabetes patients. The mechanism by which liraglutide affects the gut microbiota is not known [42].

### 3.8 | Sex and Age

Sex has been identified as an important demographic factor influencing weight loss response to GLP-1 and GIP analogs. Across several participants, younger age and female sex were significantly associated with greater weight loss [43].

## 4 | Discussion

A main thrust of this review was to gather evidence on factors that were correlated with less than favorable weight loss outcomes to GLP1 and GIP analogs. This information is important if we are to identify patients who are unlikely to respond well to management with these drugs.

The current review focused on findings from the SCALE, STEP, SUSTAIN, SURMOUNT, and SURPASS trials; this was considered high-quality evidence. Other studies that produced some primary data were cohort and retrospective studies, as well as some secondary data from reviews and conference abstracts, categorized as moderate to low quality evidence (Table 1). The inclusion of studies with weaker evidence allowed us to discern factors that should be considered for further exploration.

Studies in general considered a cut-off of  $\geq 5\%$  weight loss from baseline as successful weight loss. This cut-off arose from earlier studies on the metabolic effects of weight loss [4]. We therefore used  $< 5\%$  weight loss as our cutoff for low weight loss response. Despite this, it must be borne in mind that many patients are likely to desire higher levels of weight loss for aesthetic purposes.

From the STEP trials, we identified several factors that were correlated with low weight loss response. These factors included higher baseline body weight, BMI, HbA1c, insulin resistance, male sex, and poor adherence to medication protocols [4, 10, 18, 43]. Interestingly, the estimated reduction in expected weight loss had a dose-response relationship to baseline BMI and medication adherence [40]. These findings highlight the critical role of medication adherence in maximizing the weight loss benefits of GLP-1 receptor agonists and underscore the need for strategies to support long-term treatment persistence, such

**TABLE 1** | Ranking of evidence of studies included in the review.

Authors	Journal	Year	Title	Quality of Evidence		Main Aim	Findings	Non-responders (lost <5% body weight)
				Study design	Evidence			
Pi-Sunyer et al. [5]	The New England Journal of Medicine	2015	A randomized, controlled trial of 3.0 mg of liraglutide in weight management	Randomized controlled trial	High	This 56-week, randomized, placebo-controlled trial aimed to evaluate the efficacy and safety of 3.0 mg of liraglutide, injected subcutaneously once daily, as an adjunct to a reduced-calorie diet and increased physical activity, for weight management in overweight or obese adults who did not have diabetes at baseline.	At baseline, the mean ( $\pm$ SD) weight was 106.2 $\pm$ 21.4 kg, and the mean BMI was 38.3 $\pm$ 6.4; a total of 78.5% of the patients were women and 61.2% had prediabetes. At week 56, patients in the liraglutide group had lost a mean of 8.4 $\pm$ 7.3 kg of body weight, and those in the placebo group had lost a mean of 2.8 $\pm$ 6.5 kg (a difference of $-5.6$ kg; 95% confidence interval, $-6.0$ to $-5.1$ ; $p < 0.001$ , with last-observation-carried-forward imputation). A total of 63.2% of the patients in the liraglutide group, as compared with 27.1% in the placebo group, lost at least 5% of their body weight ( $p < 0.001$ ), and 33.1% and 10.6%, respectively, lost more than 10% of their body weight ( $p < 0.001$ ).	36.8
le Roux et al. [15]	The Lancet	2017	3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomized, double-blind trial	Randomized double-blind trial	High	In this 3-year trial, we aimed to evaluate the effect of liraglutide 3.0 mg in terms of time of onset of type 2 diabetes in individuals with prediabetes, as well as on weight loss and safety over 3 years.	The authors randomly assigned 2254 patients to receive liraglutide ( $n = 1505$ ) or placebo ( $n = 749$ ). 1128 (50%) participants completed the study up to week 160. By week 160, 26 (2%) of 1472 individuals in the liraglutide group versus 46 (6%) of 738 in the placebo group were diagnosed with diabetes while on treatment. The mean time from randomization to diagnosis was 99 (SD 47) weeks for the 26 individuals in the liraglutide group versus 87 (47) weeks for the 46 individuals in the placebo group. Taking the different diagnosis frequencies between the treatment groups into account, the time to onset of diabetes over 160 weeks among all randomized individuals was 2.7 times longer with liraglutide than with placebo (95% CI 1.9 to 3.9, $p < 0.0001$ ), corresponding with a hazard ratio of 0.21 (95% CI 0.13–0.34). Liraglutide induced greater weight loss than placebo at week 160 ( $-6.1$ [SD 7.3] vs. $-1.9$ [6.3]; estimated treatment difference $-4.3\%$ , 95% CI $-4.9$ to $-3.7$ , $p < 0.0001$ ).	N/A

(Continues)

**TABLE 1** | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Halawi et al. [16]	The Lancet	2017	Effects of liraglutide on weight, satiety, and gastric functions in obesity: a randomized, placebo-controlled pilot trial	Randomized, placebo-controlled pilot trial	High	We compared effects of liraglutide versus placebo on gastric motor functions, satiety, and weight in obese individuals over 16 weeks.	Forty [40] adults were randomly allocated (19 to the liraglutide group; 21 to the placebo group). Compared with placebo, liraglutide delayed gastric emptying of solids at 5 weeks (median 70 min [IQR 32 to 151] vs. 4 min [-21 to 18]; $p < 0.0001$ ) and 16 weeks (30.5 min [-11 to 54] vs. -1 min [-19 to 7]; $p = 0.025$ ). There was also significantly greater weight loss in the liraglutide group than in the placebo group (at 5 weeks: median 3.7 kg [IQR 2.8 to 4.8] vs. 0.6 kg [-0.3 to 1.4], $p < 0.0001$ ; at 16 weeks: 5.3 kg [5.2 to 6.8] vs. 2.5 kg [0.1 to 4.2], $p = 0.0009$ ). Satiety, as assessed by maximum tolerated volume at 16 weeks, was lower in the liraglutide group (median 750 mL [IQR 651 to 908]) compared with the placebo group (1126 mL [944–1185]; $p = 0.054$ ). No significant differences were noted between groups in terms of volume to fullness, satiety, or fasting and postprandial gastric volumes at week 16.	N/A
Goldenberg et al. [17]	Canadian Journal of Diabetes	2018	Semaglutide: review and place in therapy for adults with type 2 diabetes	Review article	High	This article overviews data from across the semaglutide clinical trial program, including efficacy and safety results and findings from post hoc analyses. The potential place of semaglutide in clinical practice is discussed.	Semaglutide is a welcome addition to the antihyperglycemic agent armamentarium in type 2 diabetes, offering robust A1C lowering and weight loss across a variety of background therapies. Semaglutide can also be considered a preferred first injectable option in the management of type 2 diabetes.	N/A
Wilding JP et al. [4]	New England Journal of Medicine	2021	Once-weekly semaglutide in adults with overweight or obesity	Randomized controlled trial	High	To assess the efficacy and safety of semaglutide in adults with overweight or obesity	Our trial showed that among adults with overweight or obesity (without diabetes), once-weekly subcutaneous semaglutide plus lifestyle intervention was associated with substantial, sustained, clinically relevant mean weight loss of 14.9%, with 86% of participants attaining at least 5% weight loss.	14
Davies M et al. [18]	The Lancet	2021	Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2)	Randomized controlled trial	High	To evaluate semaglutide's effect on weight loss in adults with overweight/obesity and type 2 diabetes	Twelve hundred and ten (1210) were randomly assigned to semaglutide 2.4 mg ( $n = 404$ ), semaglutide 1.0 mg ( $n = 403$ ), or placebo ( $n = 403$ ) and included in the intention-to-treat analysis. Estimated change in mean body weight from baseline to week 68 was -9.6% (SE 0.4) with semaglutide 2.4 mg vs. -3.4% (0.4) with placebo. Estimated treatment difference for semaglutide 2.4 mg versus placebo was -6.2 percentage points (95% CI -7.3 to -5.2; $p < 0.0001$ ). At week 68, more patients on semaglutide 2.4 mg than on placebo achieved weight reductions of at least 5% (267 [68.8%] of 388 vs. 107 [28.5%] of 376; odds ratio 4.88, 95% CI 3.58 to 6.64; $p < 0.0001$ ).	31.2

(Continues)

TABLE 1 | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Rubino D et al. [35]	JAMA	2021	Effect of continued weekly subcutaneous semaglutide vs. placebo on weight loss maintenance in adults with overweight or obesity	Randomized controlled trial	High	To assess semaglutide's effect on weight loss maintenance	Eight hundred and three (803) participants completed a 20-week run-in of subcutaneous semaglutide, 2.4 mg, with a mean weight loss of 10.6%, and were randomized to continued treatment. Semaglutide vs. placebo for an additional 48 weeks. Mean weight change was significantly different $-7.9\%$ vs. $+6.9\%$ , respectively. Among adults with overweight or obesity, maintaining treatment with subcutaneous semaglutide compared with switching to placebo resulted in continued weight loss.	11.3
Rosenstock et al. [22]	Lancet	2021	Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomized, phase 3 trial	Double-blind, randomized, placebo-controlled	High	We aimed to assess efficacy, safety, and tolerability of novel dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist tirzepatide monotherapy versus placebo in people with type 2 diabetes inadequately controlled by diet and exercise alone.	More participants on tirzepatide than on placebo met HbA1c targets of less than $7.0\%$ ( $<53$ mmol/mol; $87\%$ – $92\%$ vs. $20\%$ ) and $6.5\%$ or less ( $\leq 48$ mmol/mol; $81\%$ – $86\%$ vs. $10\%$ ) and $31\%$ – $52\%$ of patients on tirzepatide versus $1\%$ on placebo reached an HbA1c of less than $5.7\%$ ( $<39$ mmol/mol). Tirzepatide induced a dose-dependent bodyweight loss ranging from $7.0$ to $9.5$ kg.	N/A
Frias et al. [6]	The New England Journal of Medicine	2021	Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes	Open-label phase 3 trial	High	We conducted the SURPASS-2 trial (a study of Tirzepatide [LY3298176] versus semaglutide once weekly as add-on therapy to metformin in participants with type 2 diabetes) to compare the efficacy and safety of tirzepatide at doses of $5$ mg, $10$ mg, and $15$ mg with those of semaglutide at a dose of $1$ mg in patients with type 2 diabetes that had been inadequately controlled with metformin monotherapy.	At 40 weeks, reductions in the mean glycated hemoglobin level with tirzepatide at a dose of $5$ mg, $10$ mg, and $15$ mg were $-2.01$ percentage points, $-2.24$ percentage points, and $-2.30$ percentage points, respectively, as compared with $-1.86$ percentage points with semaglutide. Reductions in body weight with tirzepatide were dose-dependent. At 40 weeks, the mean reductions in body weight with tirzepatide at a dose of $5$ mg, $10$ mg, and $15$ mg were $-7.6$ kg, $-9.3$ kg, and $-11.2$ kg, respectively, as compared with $-5.7$ kg with semaglutide.	20–35
Ludvik et al. [23]	Lancet	2021	Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomized, open-label, parallel-group, phase 3 trial	Phase 3 open-label trial	High	We aimed to assess the efficacy and safety of tirzepatide versus titrated insulin degludec in people with type 2 diabetes inadequately controlled by metformin with or without SGLT2 inhibitors.	From a mean baseline HbA1c of $8.17\%$ (SD $0.91$ ), the reductions in HbA1c at week 52 were $1.93\%$ (SE $0.05$ ) for tirzepatide $5$ mg, $2.20\%$ ( $0.05$ ) for tirzepatide $10$ mg, and $2.37\%$ ( $0.05$ ) for tirzepatide $15$ mg, and $1.34\%$ ( $0.05$ ) for insulin degludec. The non-inferiority margin of $0.3\%$ was met. The estimated treatment difference (ETD) versus insulin degludec ranged from $-0.59\%$ to $-1.04\%$ for tirzepatide ( $p < 0.0001$ for all tirzepatide doses). The proportion of participants achieving a HbA1c of less than $7.0\%$ ( $<53$ mmol/mol) at week 52 was greater ( $p < 0.0001$ ) in all three tirzepatide groups ( $82\%$ – $93\%$ ) versus insulin degludec ( $61\%$ ).	N/A

(Continues)

**TABLE 1** | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Dahl et al. [24]	JAMA	2022	Effect of subcutaneous tirzepatide vs. placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes	Randomized clinical trial	High	To assess the efficacy and safety of tirzepatide added to insulin glargine in patients with type 2 diabetes with inadequate glycemic control.	In this randomized clinical trial that included 475 adults, mean change in hemoglobin HbA1c at 40 weeks was $-2.40\%$ with 10-mg tirzepatide, $-2.34\%$ with 15-mg tirzepatide, and $-0.86\%$ with placebo; the differences between each tirzepatide group vs. the placebo group were statistically significant.	N/A
De lemos et al. [25]	Circulation	2022	Effects of tirzepatide on 24-hour ambulatory blood pressure and heart rate in adults with obesity—results from the SURMOUNT-1 ambulatory blood pressure monitoring sub-study	Randomized clinical trial	High	We sought to assess the effect of tirzepatide on 24-h (24 h) mean systolic BP (SBP), diastolic BP (DBP) and HR, as measured during 24h ambulatory BP monitoring (ABPM) in people living with obesity without T2D.	Among participants randomized in the SURMOUNT-1 trial, 600 were enrolled in the ABPM substudy. No clinically significant between-treatment differences were observed in baseline characteristics. Overall, 494 participants had evaluable ABPM data at baseline and post-baseline. Treatment with all tirzepatide doses was associated with significant reductions in 24 h SBP at 36 weeks compared with placebo. Participants who received tirzepatide 5 and 10 mg, but not 15 mg, had significantly reduced 24 h DBP at 36 weeks versus placebo. An increase in 24 h HR was observed with each tirzepatide dose relative to placebo.	N/A
Krumholz et al. [26]	BMJ Heart	2024	Tirzepatide and blood pressure reduction: stratified analyses of the SURMOUNT-1 randomized controlled trial	Randomized clinical trial	High	A post hoc analysis to further explore the effects of tirzepatide on the pattern of blood pressure reduction and whether the effects were consistent across various subgroups.	Tirzepatide treatment was associated with a rapid decline in systolic and diastolic blood pressure over the first 24 weeks, followed by blood pressure stabilization until the end of the observation period, resulting in a significant net reduction by 72 weeks of 6.8 mmHg systolic and 4.2 mmHg diastolic blood pressure versus placebo. Participants randomly assigned to any tirzepatide group were more likely than those assigned to placebo to have normal blood pressure at week 72 (58.0% vs. 35.2%, respectively). Weight loss explained 68% of the systolic and 71% of the diastolic blood pressure reduction.	N/A
Hankosky et al. [27]	Journal of Pharmacology and Therapeutics	2023	Tirzepatide reduces the predicted risk of developing type 2 diabetes in people with obesity or overweight: Post hoc analysis of the SURMOUNT-1 trial	Randomized clinical trial	High	We assessed the impact of tirzepatide on 10-year predicted risk of developing type 2 diabetes (T2D) among participants in the SURMOUNT-1 trial.	Mean baseline T2D predicted risk scores did not differ between tirzepatide and placebo groups (range: 22.9%–24.3%). At week 72, mean absolute T2D predicted risk score reductions were significantly greater in tirzepatide groups (5 mg, 12.4%; 10 mg, 14.4%; 15 mg, 14.7%) versus placebo (0.7%). At week 72, median relative predicted risk reductions following tirzepatide treatment ranged from 60.3% to 69.0%. For participants with and without prediabetes, risk reductions were significantly greater in tirzepatide groups versus placebo. Conclusion: Tirzepatide treatment significantly reduced the 10-year predicted risk of developing T2D compared with placebo in participants with obesity or overweight, regardless of baseline glycemic status.	N/A

(Continues)

**TABLE 1** | (Continued)

Authors	Journal	Year	Title	Study design	Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Aronne et al. [28]	JAMA	2023	Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity	Randomized clinical trial	High	To assess the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction.	Participants were 670 women (mean weight, 107.3kg) who completed the 36-week lead-in period experienced a mean weight reduction of 20.9%. The mean percent weight change from week 36 to week 88 was -5.5% with tirzepatide vs. 14.0% with placebo (difference, -19.4% [95% CI, -21.2% to -17.7%]; $p < 0.001$ ). Overall, 300 participants (89.5%) receiving tirzepatide at 88 weeks maintained at least 80% of the weight loss during the lead-in period compared with 16.6% receiving placebo ( $p < 0.001$ ). The overall mean weight reduction from week 0 to 88 was 25.3% for tirzepatide and 9.9% for placebo. In participants with obesity or overweight, withdrawing tirzepatide led to substantial regain of lost weight, whereas continued treatment maintained and augmented initial weight reduction.	N/A
del Bosque-Plata [29]	Journal of Cellular Physiology	2021	The broad pathogenetic role of TCF7L2 in human diseases beyond type 2 diabetes	Review of association study	Medium	We aim to describe the relevance of TCF7L2 in several human disorders.	In this review, we show the association of common TCF7L2-T2D variants with many types of diseases. However, the role of rare genetic variations in the TCF7L2 gene in distinct diseases and ethnic groups has not been explored, and understanding their impact on specific phenotypes will be of clinical relevance. This offers an excellent opportunity to gain a clearer picture of the role that the TCF7L2 gene plays in the pathophysiology of human diseases. The potential pleiotropic role of TCF7L2 may underlie a possible pathway for comorbidity in human disorders.	N/A
Pilgaard et al. [30]	Nature	2009	The T allele of rs7903146 TCF7L2 is associated with impaired insulinotropic action of incretin hormones, reduced 24 h profiles of plasma insulin and glucagon, and increased hepatic glucose production in young healthy men	Association study	High	We studied the physiological, metabolic, and hormonal mechanisms underlying the elevated risk of type 2 diabetes in carriers of TCF7L2 gene.	Elevated hepatic glucose production and reduced insulinotropic effect of incretin hormones contribute to an increased risk of type 2 diabetes in carriers of the rs7903146 risk T allele of TCF7L2.	N/A
Jensterle et al. [31]	European Journal of Clinical Pharmacology	2015	Genetic variability in GLP-1 receptor is associated with inter-individual differences in weight lowering potential of liraglutide in obese women with PCOS: a pilot study	Association study	High	The potential role of genetic variability of GLP-1R on body weight response to GLP-1 RAs in obese women with polycystic ovary syndrome (PCOS) has not yet been evaluated.	GLP-1R rs10305420 polymorphism explained some of the inter-individual differences in response to liraglutide regarding weight loss in obese PCOS women.	N/A

(Continues)

**TABLE 1** | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Mosenzon O et al. [32]	Journal of the Endocrine Society	2021	Clinically relevant weight loss is achieved independently of early weight loss response to once-weekly subcutaneous semaglutide 2.4 mg (STEP 4)	Secondary analysis of RCT	Medium	To assess the relationship between early and long-term weight loss with semaglutide	In STEP 4, 902 participants initiated semaglutide at week 0, of whom 803 were randomized at week 20 (semaglutide; <i>n</i> = 535; placebo: <i>n</i> = 268; characteristics at week 0 for all randomized participants: BMI was 38.4 kg/m <sup>2</sup> ; 79.0% female; 83.7% white). For the 88.0% of participants randomized to semaglutide and who were responders at week 20, mean body weight change from week 0 to 68 was -19.7%. For non-responders at week 20, mean body weight change was -6.4% with continued semaglutide vs. -0.3% with switch to placebo. Of all participants randomized to semaglutide, 86.2% achieved a clinically relevant weight loss (≥5%) at week 68. Being a responder at week 20 was highly predictive of achieving this outcome (positive predictive value: 96.4%), whereas being a non-responder at week 20 had limited predictive value (negative predictive value: 42.9%).	13.8
Wadden et al. [33]	JAMA	2021	Effect of subcutaneous semaglutide vs. placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity	Randomized controlled trial	High	In adults with overweight or obesity without diabetes, what effect does once-weekly subcutaneous semaglutide, 2.4 mg, have on body weight when added to intensive behavioral therapy with an initial low-calorie diet?	Among adults with overweight or obesity, once-weekly subcutaneous semaglutide, compared with placebo, used as an adjunct to intensive behavioral therapy and initial low-calorie diet, resulted in significantly greater weight loss during 68 weeks. Further research is needed to assess the durability of these findings.	N/A
Garvey WT et al. [34]	Nature Medicine	2022	Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial	Randomized controlled trial	High	To evaluate the long-term effects of semaglutide on weight loss	The STEP 5 trial assessed the efficacy and safety of once-weekly subcutaneous semaglutide 2.4 mg versus placebo (both plus behavioral intervention) for long-term treatment of adults with obesity, or overweight with at least one weight-related comorbidity, without diabetes. Adults with overweight (with at least one weight-related comorbidity) or obesity, semaglutide treatment led to substantial, sustained weight loss over 104 weeks versus placebo. The mean change in body weight from baseline to week 104 was -15.2% in the semaglutide group ( <i>n</i> = 152) versus -2.6% with placebo ( <i>n</i> = 152), for an estimated treatment difference of -12.6% points (95% confidence interval, -15.3 to -9.8; <i>p</i> < 0.0001). More participants in the semaglutide group than in the placebo group achieved weight loss ≥5% from baseline at week 104 (77.1% versus 34.4%; <i>p</i> < 0.0001).	12.6

(Continues)

TABLE 1 | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Rubino et al. [35]	JAMA	2021	Effect of continued weekly subcutaneous semaglutide vs. placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial	Randomized controlled trial	High	The STEP 4 withdrawal trial was conducted to compare the effect of continuing once-weekly treatment with subcutaneous semaglutide, 2.4 mg, vs. switching to placebo (both with lifestyle intervention) on body weight in participants with overweight/obesity who reached a semaglutide treatment dosage of 2.4 mg once weekly during an initial 20-week run-in.	Among 803 study participants who completed the 20-week run-in period (with a mean weight loss of 10.6%) and were randomized (mean age, 46 [SD, 12] years; 634 [79%] women; mean body weight, 107.2 kg [SD, 22.7 kg]), 787 participants (98.0%) completed the trial and 741 (92.3%) completed treatment. With continued semaglutide, mean body weight change from week 20 to week 68 was -7.9% vs. +6.9% with the switch to placebo (difference, -14.8 [95% CI, -16.0 to -13.5] percentage points; $p < 0.001$ ). Waist circumference (-9.7 cm [95% CI, -10.9 to -8.5 cm]), systolic blood pressure (-3.9 mmHg [95% CI, -5.8 to -2.0 mmHg]), and SF-36 physical functioning score (2.5 [95% CI, 1.6-3.3]) also improved with continued subcutaneous semaglutide vs. placebo (all $p < 0.001$ ). Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4 mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.	22.1
Pratley RE et al. [36]	The Lancet Diabetes & Endocrinology	2018	Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7)	Randomized controlled trial	High	To compare the efficacy of semaglutide and dulaglutide in type 2 diabetes	Twelve hundred and one (1201) patients were randomly assigned to treatment; of these, 301 were exposed to semaglutide 0.5 mg, 299 to dulaglutide 0.75 mg, 300 to semaglutide 1.0 mg, and 299 to dulaglutide 1.5 mg. From overall baseline mean, mean percentage HbA1c was reduced by 1.5 (SE 0.06) percentage points with semaglutide 0.5 mg versus 1.1 (0.05) percentage points with dulaglutide 0.75 mg (estimated treatment difference [ETD] -0.40 percentage points [95% CI -0.55 to -0.25]; $p < 0.0001$ ) and by 1.8 (0.06) percentage points with semaglutide 1.0 mg versus 1.4 (0.06) percentage points with dulaglutide 1.5 mg (ETD -0.41 percentage points [-0.57 to -0.25]; $p < 0.0001$ ). From overall baseline mean, mean body weight was reduced by 4.6 kg (SE 0.28) with semaglutide 0.5 mg compared with 2.3 kg (0.27) with dulaglutide 0.75 mg (ETD -2.26 kg [-3.02 to -1.51]; $p < 0.0001$ ) and by 6.5 kg (0.28) with semaglutide 1.0 mg compared with 3.0 kg (0.27) with dulaglutide 1.5 mg (ETD -3.55 kg [-4.32 to -2.78]; $p < 0.0001$ ).	N/A

(Continues)

**TABLE 1** | (Continued)

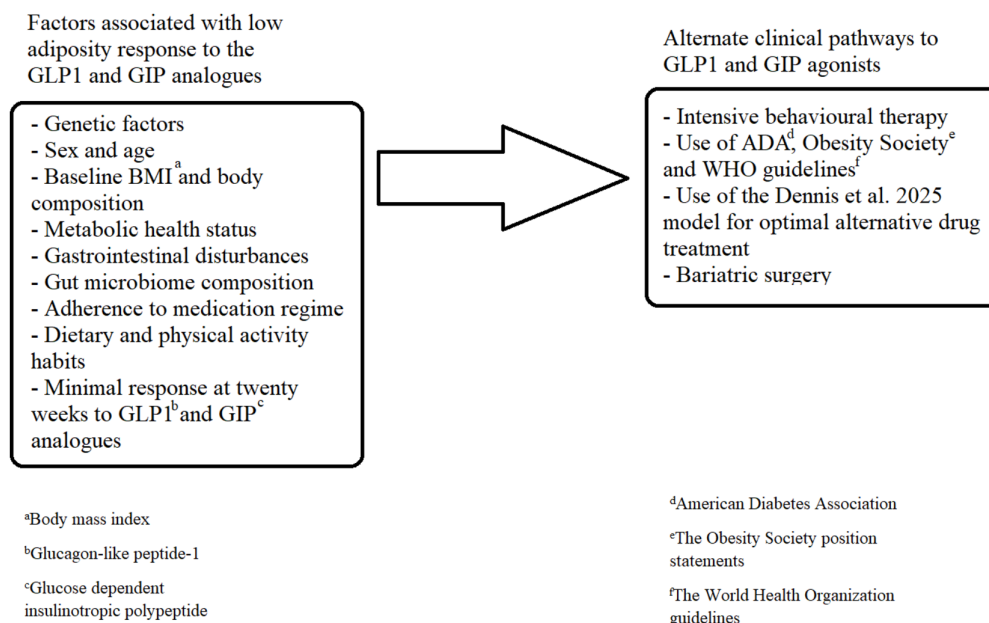
Authors	Journal	Year	Title	Quality of Evidence		Main Aim	Findings	Non-responders (lost <5% body weight)
				Study design	Evidence			
Del Prato [37]	Lancet	2021	Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomized, open-label, parallel-group, multicenter, phase 3 trial	Randomized controlled trial	High	To assess efficacy and safety, with a special focus on cardiovascular safety, of the novel dual GIP and GLP-1 receptor agonist tirzepatide versus insulin glargine in adults with type 2 diabetes and high cardiovascular risk inadequately controlled on oral glucose-lowering medications.	Of 3045 participants screened, 2002 participants were randomly assigned to tirzepatide or glargine. 1995 received at least one dose of tirzepatide 5 mg ( <i>n</i> = 329, 17%), 10 mg ( <i>n</i> = 328, 16%), or 15 mg ( <i>n</i> = 338, 17%), or glargine ( <i>n</i> = 1000, 50%), and were included in the modified intention-to-treat population. At 52 weeks, mean HbA1c changes with tirzepatide were $-2.43\%$ (SD 0.05) with 10 mg and $-2.58\%$ (0.05) with 15 mg, versus $-1.44\%$ (0.03) with glargine. The estimated treatment difference versus glargine was $-0.99\%$ (multiplicity adjusted 97.5% CI $-1.13$ to $-0.86$ ) for tirzepatide 10 mg and $-1.14\%$ ( $-1.28$ to $-1.00$ ) for 15 mg, and the non-inferiority margin of 0.3% was met for both doses. Adjudicated MACE-4 events (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) occurred in 109 participants and were not increased on tirzepatide compared with glargine (hazard ratio 0.74, 95% CI 0.51–1.08). 60 deaths ( <i>n</i> = 25 [3%] tirzepatide; <i>n</i> = 35 [4%] glargine) occurred during the study.	N/A
Matikainen et al. [38]	Diabetes	2013	GLP-1 responses are heritable and blunted in acquired obesity with high liver fat and insulin resistance	Association study	Medium	Among 35 monozygotic (MZ) and 75 dizygotic (DZ) twin pairs (discordant and concordant for obesity), the authors sought to determine the heritability of glucagon-like peptide 1 (GLP-1) responses to an oral glucose tolerance test (OGTT) and the influence of acquired obesity on GLP-1, glucose-dependent insulinotropic peptide (GIP), and peptide YY (PYY) during OGTT or meal test.	The heritability of GLP-1 area under the curve was 67% (95% CI 45–80). Cotwins from weight-concordant MZ and DZ pairs and weight-discordant MZ pairs but concordant for liver fat content demonstrated similar glucose, insulin, and incretin profiles after the OGTT and meal tests. In contrast, higher insulin responses and blunted 60-min GLP-1 responses during the OGTT were observed in the heavier as compared with leaner MZ cotwins discordant for BMI, liver fat, and insulin sensitivity. Blunted GLP-1 response to OGTT was observed in heavier as compared with leaner DZ cotwins discordant for obesity and insulin sensitivity.	N/A
Weiss T et al. [39]	BMI Open Diabetes Research and Care	2022	Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK	Observational study	Medium	To evaluate real-world outcomes of GLP-1 receptor agonists in type 2 diabetes	Among 589 patients initiating a GLP-1 RA, the median body mass index was 41.2 kg/m <sup>2</sup> (IQR [35.8, 46.4]). Among patients with weight measures available ( <i>n</i> = 341 at 12 months; <i>n</i> = 232 at 24 months), 33.4% and 43.5% achieved weight loss $\geq 5\%$ of baseline weight at 12 and 24 months, respectively. At 12 and 24 months, 64.5% and 59.2% were adherent, and 45.2% and 64.7% discontinued, respectively. A minority of patients initiating GLP-1 RAs achieved $\geq 5\%$ weight loss, suggesting the real-world benefit of these agents on weight loss may be lower than that observed in clinical trials. Patients on GLP-1 RAs may benefit from additional support to improve long-term adherence.	56.5

(Continues)

TABLE 1 | (Continued)

Authors	Journal	Year	Title	Study design	Quality of Evidence	Main Aim	Findings	Non-responders (lost <5% body weight)
Lingway I et al. [40]	The Lancet	2022	Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation	Review/ Opinion	Lower	To review the clinical evidence supporting weight loss as a fundamental target, propose a novel therapeutic framework, and explore challenges for the widespread implementation of this approach for people with type 2 diabetes.	Weight loss is known to reverse the underlying metabolic abnormalities of type 2 diabetes and, as such, improve glucose control; loss of 15% or more of body weight can have a disease-modifying effect in people with type 2 diabetes, an outcome that is not attainable by any other glucose-lowering intervention. Furthermore, weight loss in this population exerts benefits that extend beyond glycaemic control to improve risk factors for cardiometabolic disease and quality of life. We review the evidence supporting the role of weight loss in the management of type 2 diabetes and propose that many patients with type 2 diabetes would benefit from having a primary weight-centric approach to diabetes treatment.	N/A
Shang J et al. [42]	PeerJ	2021	Liraglutide-induced structural modulation of the gut microbiota in patients with type 2 diabetes mellitus	Observational study	Medium	To assess liraglutide's effect on gut microbiota in type 2 diabetes	In the present study, 40 patients with T2DM were treated with liraglutide for 4 months. Fecal samples and clinical characteristics were collected from these 40 T2DM patients before and after the liraglutide treatment. The diversity and composition of gut microbiota in the two groups were determined by sequencing the V4 region of bacterial 16S rRNA genes. Meanwhile, blood glucose, insulin, hemoglobin A1c (HbA1c), and lipid metabolism were also measured in the pre- and post-liraglutide-treatment groups. Baseline HbA1c was associated with liraglutide treatment response ( $R^2 = 0.527, \beta = -0.726, p < 0.0001$ ). After adjusting for baseline HbA1c, blood urea nitrogen was associated with liraglutide treatment response. Results showed reduced gut microbial alpha diversity, different community structure distribution, and altered microbial interaction network in patients treated with liraglutide. This study suggests that baseline HbA1c, blood urea nitrogen, and gut microbiota are associated with the liraglutide treatment applied to patients with T2DM. These findings may contribute to the beneficial effects of liraglutide against diabetes.	N/A
Kushner RF et al. [43]	Journal of the Endocrine Society	2021	Once-weekly subcutaneous semaglutide 2.4 mg reduces body weight in adults with overweight or obesity regardless of baseline characteristics (STEP 1)	Secondary analysis of RCT	Medium	To assess semaglutide's effect on weight loss across different baseline characteristics	STEP 1 included 1961 randomized participants (mean age 46 years, body weight 105.3 kg, BMI 37.9 kg/m <sup>2</sup> , 74.1% female). For categorical weight loss, the observed proportions of participants with $\geq 20\%$ , $15 \leq 20\%$ , $10 \leq 15\%$ , and $5 \leq 10\%$ weight loss at week 68 were 34.8%, 19.9%, 20.0%, and 17.5% with semaglutide vs. 2.0%, 3.0%, 6.8%, and 21.2% with placebo, respectively. The distribution of participants across weight loss groups did not appear to be affected by any baseline characteristics, except sex and baseline body weight. Sex and baseline body weight were independently associated with weight loss with semaglutide vs. placebo at week 68 ( $p < 0.001$ for both tests for subgroup interactions).	N/A

Abbreviations: BMI, body mass index; GIP, glucose-dependent insulinotropic polypeptide; GLP1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin test; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; RCT, random control trial; T2DM, type 2 diabetes mellitus.



**FIGURE 2** | Emergent factors associated with poor GLP1 (glucagon-like peptide-1 receptor agonist) and GIP (glucose-dependent insulinotropic polypeptide) response and alternate pathways.

as patient education, side effect management, and regular follow-up [11].

Genetic factors among women with polycystic PCOS influenced responses to GLP-1 and GIP analogs [29, 30]. In addition, a common variant of the GLP1R gene (rs10305420) was associated with less weight loss with liraglutide treatment. This polymorphism explained some of the interindividual differences in response to liraglutide with respect to weight loss [31]. This highlights the potential for polygenic prediction models to inform personalized treatment decisions. Further research is needed to fully understand the implications of these genetic factors on the efficacy of GLP-1 and GIP analogs [44, 45].

The findings from body composition studies are important. The studies of BMI suggest that, while individuals with higher baseline BMI may experience larger absolute weight reductions, they may require higher doses or longer treatment durations to achieve clinically meaningful percentage weight loss. The mechanisms underlying this association are not fully understood, but may involve differences in drug distribution, metabolism, or target receptor expression in individuals with severe obesity [46]. These findings highlight the limitations of using scale weight alone to assess treatment response and suggest that preserving lean mass may be an important goal of obesity pharmacotherapy.

Metabolic health status was also important, such that those with higher baseline fasting plasma glucose lost less weight in a trial of tirzepatide [47]. These findings suggest that individuals with poorer glycemic control at baseline may require higher doses or combination therapies to achieve optimal weight loss outcomes.

Insulin resistance has also been identified as a predictor of weight loss response to GLP-1 and GIP analogs [36]. The mechanisms linking insulin resistance to attenuated weight loss response are not fully elucidated but may involve impaired GLP-1

receptor signaling or altered energy metabolism in insulin-resistant states [46].

Taken together, these findings highlight the complex interplay between obesity and metabolic health in the context of GLP-1 and GIP analog therapy. While these medications can effectively improve glycemic control and insulin sensitivity, preexisting metabolic dysregulation may limit their weight loss efficacy in some individuals. Personalized treatment strategies, such as dose escalation, combination therapy, or adjunctive lifestyle interventions, may be necessary to optimize outcomes in patients with poor metabolic health at baseline.

#### 4.1 | Adherence to Medication Regimen

Adults who exhibited high adherence to drug regimens achieved significantly greater weight loss compared with those with low adherence. High adherence was associated with a 2.1 percentage point greater weight loss (95% CI, 1.7 to 2.5) compared with low adherence [39]. In addition, Lingvay et al. provided compelling real-world evidence on the importance of medication adherence for weight loss outcomes with semaglutide. There was a strong dose-response relationship between treatment duration and weight loss; each additional month of treatment was associated with a 0.6 percentage point greater weight loss (95% CI, 0.5 to 0.7) [40].

Lifestyle factors, such as dietary habits and physical activity, can modulate weight loss responses to GLP-1 and GIP analogs. These findings suggest that the appetite-suppressing effects of semaglutide may facilitate changes in dietary habits that enhance weight loss outcomes. Participants using semaglutide who undertook physical activity showed superior weight loss compared with those with low physical activity. These findings highlight the synergistic effects of pharmacotherapy and lifestyle modification for optimizing weight loss outcomes. Of note also was the fact that consumption of high-energy-density food

and low levels of activity reduced the weight loss response to the GLP1 and GIP analogs [4].

Tirzepatide has shown very promising results in weight reduction and glycemic control across various trials, with its dual mechanism of action targeting both GIP and GLP-1 receptors. The SURMOUNT and SURPASS trials have provided extensive data on its efficacy, safety, and potential predictors of response, contributing to a better understanding of its role in managing obesity and type 2 diabetes.

## 4.2 | Gut Microbiome Composition

The gut microbiome has emerged as a potential mediator of weight loss response to GLP-1 and GIP analogs [41, 42]. Animal studies indicate that the addition of probiotics can improve the action of GLP-1 and GIP agonists [48]. The mechanism by which GLP-1 analogs affect the gut microbiota is not known [42]. Mechanistically, animal studies point to the increased production of short-chain fatty acids (SCFAs) with liraglutide [49]. They are thought to modulate energy metabolism and appetite regulation through effects on G protein-coupled receptors and the gut-brain axis [50]. The evidence among humans is lacking [51].

Collectively, these studies highlight the potential of the gut microbiome as a biomarker and therapeutic target for personalized obesity management. Strategies to modulate the gut microbiome, such as prebiotic or probiotic interventions, may enhance the weight loss efficacy of GLP-1 and GIP analogs in some individuals. However, further research is needed to validate these findings in larger and more diverse populations, and to elucidate the optimal approaches for microbiome-based precision medicine.

The mechanisms underlying these age and sex differences are not fully understood but may involve variations in body composition, hormonal milieu, or drug pharmacokinetics [4]. For example, older individuals tend to have higher proportions of visceral fat and lower muscle mass, which may limit the weight loss efficacy of GLP-1 and GIP analogs. Hormonal changes during menopause, such as declines in estrogen and increases in androgen levels, may also modulate the response to these medications.

Despite the general trends, it is important to note that GLP-1 and GIP analogs can be effective for weight loss across a wide range of ages and in both sexes. Nevertheless, there appear to be age and sex effects such that older age and male sex are associated with lower weight loss [43].

While age and sex may influence the magnitude of weight loss response to GLP-1 and GIP analogs, these factors should not preclude the use of these medications in any particular demographic group. Personalized dose adjustments, monitoring, and side effect management may help to optimize outcomes and mitigate any potential age- or sex-related differences in treatment response.

## 4.3 | Clinical Implications

Physicians who manage obese patients must struggle with the fact that the cutoff of  $\geq 5\%$  weight loss is metabolically

important, while at the same time is not in keeping with many patients' expectations. It is important, therefore, for physicians to use the current information to modulate their expectations while helping them to set realistic goals.

Our review revealed some important factors that would place patients into a nonresponse to GLP1 and GIP analogs category for obesity. However, patients may have a complex metabolic picture, such as elevated levels of cortisol (that may be associated with chronic psychiatric or psychological triggers). Such patients would need simultaneous management of their psychiatric or psychological conditions in order to change the hormonal milieu that undoubtedly contributes to the maintenance of higher body adiposity/weight, despite the presence of the incretin analogs.

Other scenarios would include factors such as severe obesity, where the average weight loss associated with the drug does not provide an obesity related clinically or aesthetically important change to the patient. The evidence suggests that, in response to the incretin analogs, glycemic control is achievable at a lower dose and more readily than obesity management. It might therefore be expedient in some cases to recommend glycemic stabilization as a primary goal as opposed to maintenance of an appreciably lower level of obesity. In addition, patients with severe metabolic disease may be referred to bariatric surgery as an ultimate management strategy.

One of the striking associations of low response to GLP1 and GIP analogs has been little change in the initial 21-week period of drug administration. This should help to guide a clinician to seek established alternative drugs or bariatric surgery. Of course, the age of the patient and the level of their comorbidities would influence alternative interventions. Yet the use of incretin analogs and their association with improved general metabolic health may help to prepare a patient for an intervention such as bariatric surgery. Figure 2 presents factors that the current review has revealed as potential predictors of low response and possible methods of amelioration. This can be used for guidance when taking history and providing treatment plans for patients.

The effect of genetic screening must be handled carefully, as it can communicate a level of futility to the patient. It must be borne in mind that genes require environmental triggers for expression. In many cases, the presence of a gene does not preclude one from a positive response to treatment protocols. Such patients may be encouraged to try this class of drugs at least for a 20-week run-in period.

Less difficult, possibly modifiable challenges are those such as gastrointestinal disturbance; these may be approached by smaller increments in the dosage. Also, appropriately counseled patients may be willing to accept glycemic control as their primary outcome.

Progressive healthcare systems may consider screening among young and non-diseased patients to help identify those who may be at risk of metabolic disturbances, including elevated insulin resistance and glycemia as assessed by HbA1c. This allows the clinician to intervene at an early stage with the incretin analogs. Where the patient is not obese, dosages can be kept low, hopefully producing fewer side effects.

The guidelines of societies such as the American Diabetes Association, the World Health Organization, and others should be used by treating clinicians. It is important that the clinician keeps up to date with the recommendations, as guidelines in this emerging and exciting field tend to change frequently [52].

Factors such as the cost of drugs and lack of insurance coverage can be prohibitive, and the use of alternatives such as compounding pharmacies may help to address these situations. Drug management of diabetes should include factors emerging from Dennis et al. (2025)'s model, a five-drug class model using routinely available clinical features. This is important because it makes use of routinely available clinical features to optimize prescribing in type 2 diabetes [53].

Figure 2 presents factors associated with low response to the incretin analogs and proposes some alternative approaches.

#### 4.4 | Further Research

As the field of obesity pharmacotherapy continues to evolve, it will be crucial to validate the predictors in larger and more diverse populations and to develop practical tools for integrating them into clinical decision-making. Equally important will be the investigation of novel strategies for optimizing weight loss response, such as combination therapies, microbiome modulation, and precision nutrition approaches.

Ultimately, the goal of this research is to enable a more personalized and effective approach to obesity management, one that takes into account the unique characteristics and needs of each individual patient. By moving beyond a one-size-fits-all paradigm and embracing the complexity of obesity pathophysiology, we can improve outcomes, reduce disparities, and alleviate the enormous burden of this chronic disease on patients, healthcare systems, and society as a whole.

#### 5 | Conclusion

In summary, we provide a comprehensive overview of the current state of knowledge on predictors of low weight loss response to GLP-1 and GIP analogs. By incorporating the latest evidence from clinical trials, reviews, and mechanistic studies, it highlights the complex interplay of genetic, metabolic, microbial, and lifestyle factors that influence treatment outcomes.

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#### Conflicts of Interest

The authors declare no conflicts of interest.

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