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From GLP-1 Agonism to Triple-Receptor Therapy. Narrative Review of Semaglutide, Tirzepatide, and Retatrutide in Obesity Management

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Background: Obesity is a chronic multifactorial disease that affects a growing proportion of the global population. According to the WHO, obesity is now a global concern. From 1990 to 2022, the prevalence of obesity among minors increased from 2% to 8%, and among adults, it rose from 7% to 16%. The growing global prevalence of obesity has intensified the need for pharmacological therapies.

Aim: This narrative review presents the clinical efficacy, metabolic effects, and safety profiles of semaglutide, tirzepatide, and retatrutide, with particular emphasis on their underlying mechanisms of action.

Materials and Methods: A narrative review was conducted based on key randomised controlled trials, including the STEP, SURMOUNT, and phase II retatrutide programs. Data on weight reduction, metabolic parameters, and adverse events were extracted and analysed. Mechanistic insights were integrated to interpret differences in clinical outcomes.

Results: All three therapies produced significant weight reduction and metabolic improvements, with efficacy increasing in relation to the number of targeted receptors. Semaglutide resulted in a weight loss of up to 16.0%, tirzepatide achieved a reduction of 20.9%, and retatrutide demonstrated the highest efficacy, with a weight loss of 24.2%. All agents were associated with improvements in cardiac, glycemic, and lipid profiles. Gastrointestinal adverse events were frequent and dose-dependent, resulting in higher discontinuation rates at higher doses.

Conclusions: Incretin agonists represent a significant advancement in obesity pharmacotherapy, with multi-receptor targeting translating into superior metabolic outcomes. Retatrutide demonstrates the highest potential efficacy among studied agents, although further phase III data are required. These findings support the concept that obesity is a chronic disease that requires long-term treatment and highlight the growing role of mechanism-based pharmacotherapy in its management.

Keywords: obesity, incretin-based therapy, GLP-1 receptor agonists, dual agonists, triple agonists, semaglutide, tirzepatide, retatrutide

1. Introduction

Obesity is a disease that affects a growing proportion of the global population. According to the World Health Organisation (WHO), obesity is now a global health concern, rather than being limited to high-income countries. From 1990 to 2022, the prevalence of obesity among minors increased from 2% to 8%, and among adults aged 18 and older, it rose from 7% to 16% (World Health Organization, n.d.). These trends are supported by an analysis from the NCD Risk Factor Collaboration published in The Lancet, which synthesised data from 3,663 population-representative studies and confirmed a consistent global rise in obesity, with few exceptions. Addressing these trends requires the development and evaluation of more effective pharmacological interventions, alongside educational initiatives and the promotion of healthy lifestyles, as key components of the global strategy to combat the obesity epidemic (Phelps et al., 2024). The anticipated increase in the proportion of individuals with obesity, as opposed to

those who are merely overweight, highlights the urgent need for novel therapeutic approaches. While preventive strategies are still essential, the rising number of patients classified as clinically obese warrants an intensified focus on developing modern pharmacological approaches to aid in their treatment (Welsh et al., 2024). Obesity is recognized as a chronic, multifactorial disease with a complex metabolic background that has systemic effects on multiple organ systems. The excessive accumulation of adipose tissue leads to the development of insulin resistance, chronic low-grade inflammation, and disturbances in lipid metabolism. These factors are key mechanisms behind many complications related to obesity. Among the most significant metabolic outcomes are type 2 diabetes and nonalcoholic fatty liver disease (NAFLD), where insulin resistance and systemic inflammation play central roles in disease progression. Obesity is also strongly associated with dyslipidemia and hypertension, which significantly increase the risk of cardiovascular diseases, including coronary artery disease and stroke, both of which remain leading causes of mortality worldwide(Lu et al., 2014; Powell-Wiley et al., 2021; Rodriguez et al., 2021; Zelber-Sagi et al., 2012). Beyond cardiometabolic disorders, obesity can contribute to respiratory complications such as obstructive sleep apnea, obesity hypoventilation syndrome, asthma and COPD(Felson et al., 1997; Haase et al., 2021; Wang et al., 2020). Mechanical overload predisposes joints to degenerative diseases, including osteoarthritis and injuries (Felson et al., 1997; Jordan et al., 2007). Furthermore, growing evidence suggests a connection between obesity and an elevated risk of several cancers, highlighting the systemic and multifaceted nature of the disease (Bjørge et al., 2019; M. Sun et al., 2024). The cumulative burden of these complications not only reduces life expectancy and impairs quality of life but also places considerable strain on healthcare systems. Given the projected rise in the number of individuals classified as clinically obese beyond just those considered overweight, the need for effective therapeutic strategies is becoming increasingly urgent (Arterburn et al., 2005; Finkelstein et al., 2005). While lifestyle-based preventive measures are vital in addressing the global obesity epidemic, the increasing number of patients with established obesity calls for intensified efforts to develop and implement modern pharmacological interventions alongside public health initiatives. This narrative review aims to summarize and synthesize clinical evidence from key randomized controlled trials evaluating the efficacy, metabolic benefits, and safety profiles of retatrutide, tirzepatide, and semaglutide in adults with obesity, with or without type 2 diabetes. Given the global burden of obesity and the limitations of existing therapies, these novel peptide-based agents represent promising interventions. This review synthesizes clinical evidence from pivotal trials to evaluate their effects on weight reduction, glycemic control, and metabolic outcomes, providing insights into their potential role in contemporary obesity management.

2. Mechanism

Glucagon-like peptide-1 (GLP-1) is a hormone produced by L cells in the small intestine in response to food intake. It acts through the GLP-1 receptor (GLP-1R), which is a G protein-coupled receptor (GPCR) found on pancreatic beta cells, among other cell types. When GLP-1R is activated, it increases the levels of cyclic adenosine monophosphate (cAMP) inside the cells, leading to enhanced insulin secretion in a glucose-dependent manner while also inhibiting glucagon secretion. This results in lower blood sugar levels, particularly after meals.

Additionally, GLP-1 slows gastric emptying and influences mechanisms in the brain that promote a sense of fullness, which can aid in weight loss (Kowalska et al., 2026). A key limitation of native GLP-1 is its very short half-life, which is due to rapid enzymatic degradation by DPP-4. This enzyme cleaves the dipeptide at the N-terminus, specifically at the positions of Ala8 and Glu9. Research has shown that the absence of DPP-4 protection significantly shortens the duration of action of GLP-1 analogues in vivo. This has been confirmed by comparing molecules that are susceptible to DPP-4 cleavage with those that are resistant. Therefore, the primary goal in designing GLP-1 analogues has been to create molecules that maintain a high affinity for the GLP-1 receptor while also demonstrating resistance to enzymatic degradation, thereby ensuring prolonged systemic exposure (Lau et al., 2015). GLP-1 receptor agonists are an effective therapeutic option for the treatment of type 2 diabetes and obesity. Exenatide was the first drug in this class approved for clinical use in 2005, followed by liraglutide in 2009. New-generation GLP-1 analogues, including albiglutide and dulaglutide, combine larger proteins (immunoglobulins and albumin) with two modified, DPP4-resistant GLP-1 molecules, representing a significant advance due to their extended half-lives, which allow for once-weekly dosing (Brønden et al., 2015; Jimenez-Solem et al., 2010). A major pharmaceutical advancement in semaglutide development was the introduction of an oral formulation co-administered with sodium N-(8-[2-hydroxybenzoyl amino) caprylate (SNAC), an absorption enhancer. As a peptide, semaglutide is otherwise susceptible to enzymatic degradation and exhibits limited epithelial permeability in the gastrointestinal tract. SNAC promotes transcellular absorption through the gastric mucosa by locally increasing mucosal permeability and establishing a transient, pH-buffering microenvironment that protects the molecule from proteolytic degradation. This combined formulation enables effective oral administration of semaglutide (Buckley et al., 2018).

3. Clinical studies

In the STEP 1 study, 1,961 non-diabetic adults with a body mass index (BMI) greater than 30 kg/m², or greater than 27 kg/m² with one or more weight-related health conditions, were randomly assigned in a 2:1 ratio to receive either once-weekly subcutaneous semaglutide at a dose of 2.4 mg or a placebo. This was combined with a lifestyle intervention and lasted for 68 weeks. Participants receiving semaglutide experienced a sustained and clinically significant mean weight loss of 14.9%, compared to 2.4% in the placebo group. A substantial proportion of semaglutide-treated participants reached clinically meaningful weight-loss thresholds of ≥5%, ≥10%, and ≥15%, highlighting the robust efficacy of this therapy. Furthermore, semaglutide treatment was linked to improvements in cardiometabolic health and exercise parameters, indicating benefits beyond weight loss alone. The safety profile of semaglutide was similar to that of other GLP-1 receptor agonists, with gastrointestinal side effects such as nausea, diarrhoea, vomiting, and constipation. These occurred more frequently in participants receiving semaglutide compared to those receiving placebo (74.2% and 47.9%). However, these side effects were generally mild to moderate and transient. Overall, these results indicate that semaglutide is an effective treatment for obesity and serve as a benchmark for assessing the efficacy of future peptide-based therapies (Wilding et al., 2021). In STEP 4 and the

extension of STEP 1, the durability of treatment effects was evaluated. Those who continued treatment maintained and even improved their weight loss, while those who stopped experienced significant weight regain. The STEP 1 extension revealed that after one year, participants retained only about one-third of their initial weight loss, leading to a reduction of 5.6% at week 120 (Wilding et al., 2022).

In the STEP 2 trial, a phase 3, double-blind, double-dummy study, 1,595 adults with overweight or obesity (BMI ≥27 kg/m²) and type 2 diabetes (HbA1c 7–10%) were enrolled. Of these participants, 1,210 were randomized to receive either once-weekly subcutaneous semaglutide at doses of 2.4 mg (n=404), 1.0 mg (n=403), or a placebo (n=403) for 68 weeks, along with lifestyle interventions. At week 68, the mean reduction in body weight was 9.6% for those taking semaglutide 2.4 mg, compared to 3.4% for the placebo group, while the 1.0 mg dose resulted in a 7.0% reduction. The estimated treatment difference between the semaglutide 2.4 mg group and the placebo was -6.2 percentage points ($p<0.0001$), and -2.7 percentage points compared to the 1.0 mg group. A significantly larger proportion of participants receiving semaglutide 2.4 mg achieved clinically meaningful weight-loss thresholds of ≥5%, ≥10%, ≥15%, and ≥20% compared to both the semaglutide 1.0 mg and placebo groups. In addition to weight reduction, semaglutide also improved glycemic control. HbA1c levels decreased by 1.6 percentage points with the 2.4 mg dose, compared to a 0.4 percentage point reduction in the placebo group. A higher proportion of participants reached HbA1c targets of ≤6.5% or <7.0%. Improvements in fasting glucose levels were also more pronounced in the semaglutide groups. Additionally, reductions in the use of concomitant glucose-lowering medications were more common with semaglutide 2.4 mg (28.6%) than with semaglutide 1.0 mg (25.1%) or placebo (7.1%). Beyond glycemic parameters, positive effects were noted in cardiometabolic markers, inflammation levels, and measures of physical function. Adverse events were reported more frequently among participants taking semaglutide 2.4 mg (87.6%) and 1.0 mg (81.8%) compared to placebo (76.9%), with gastrointestinal events being the most common and generally mild to moderate in severity. Overall, the STEP 2 trial demonstrates that semaglutide 2.4 mg leads to clinically meaningful weight loss and significant metabolic improvements in individuals with obesity and type 2 diabetes, extending the efficacy observed in non-diabetic populations from the STEP 1 trial (Davies et al., 2021).

The STEP 3 trial was a 68-week, randomized, double-blind, placebo-controlled phase 3a study that enrolled 611 adults without diabetes who were either overweight (BMI ≥27 kg/m² with at least one weight-related comorbidity) or obese (BMI ≥30 kg/m²). Participants were randomly assigned in a 2:1 ratio to receive either once-weekly subcutaneous semaglutide at a dose of 2.4 mg (n=407) or a placebo (n=204). Both groups engaged in an intensive lifestyle intervention, which included an initial 8-week low-calorie diet followed by 30 sessions of intensive behavioural therapy over the 68 weeks. At the end of the study (week 68), participants taking semaglutide experienced an average body weight reduction of -16.0%, compared to a -5.7% reduction for those on placebo. This resulted in an estimated treatment difference of -10.3 percentage points ($p<0.001$). A significantly larger proportion of participants receiving semaglutide achieved clinically meaningful weight-loss milestones. Specifically, 86.6% of the semaglutide group achieved a weight reduction of at least 5%, compared to 47.6% in the

placebo group. For the thresholds of at least 10% and 15% weight loss, 75.3% of the semaglutide group met these goals versus 27.0% in the placebo group, and 55.8% versus 13.2%, respectively. Semaglutide also demonstrated positive effects on cardiometabolic and physical performance metrics compared to the placebo. Overall, the rates of adverse events were similar between the two groups; however, gastrointestinal events were more common in the semaglutide group (82.8%) compared to the placebo group (63.2%). Common adverse events included nausea, diarrhoea, constipation, and vomiting, which were generally mild to moderate and transient. Permanent discontinuation due to adverse events occurred in 6.4% of participants receiving semaglutide and 2.9% of those receiving placebo (Wadden et al., 2021).

The STEP-up 3B trial was a 72-week, randomized, double-blind, placebo-controlled study examining a higher dose of semaglutide (7.2 mg) in adults with obesity (BMI ≥30 kg/m²) who did not have diabetes. Out of 1,529 individuals screened, 1,407 were randomly assigned in a 5:1:1 ratio to receive either once-weekly subcutaneous semaglutide 7.2 mg (n=1,005), semaglutide 2.4 mg (n=201), or a placebo (n=201). All participants followed a lifestyle intervention that included a 500 kcal/day energy deficit and a minimum of 150 minutes of physical activity per week. At the end of week 72, the average weight reduction was -18.7% for participants taking semaglutide 7.2 mg, compared to -15.6% for those on 2.4 mg and -3.9% for the placebo group. The estimated treatment difference between the 7.2 mg and 2.4 mg groups was -3.1 percentage points ($p<0.0001$), and the difference versus placebo was -14.8 percentage points ($p<0.0001$). According to the trial product estimate, weight reductions were -20.7% for 7.2 mg, -17.5% for 2.4 mg, and -2.4% for placebo. A significantly larger proportion of participants who received 7.2 mg achieved clinically meaningful weight-loss thresholds. Nearly half (47.7%) experienced a weight loss of at least 20%, compared to 33.3% in the 2.4 mg group and 2.9% in the placebo group. Additionally, 31.2% of participants taking 7.2 mg achieved a weight loss of 25% or more, while 15.3% in the 2.4 mg group reached this threshold, and none in the placebo group did. The likelihood of achieving weight loss of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% was significantly higher with 7.2 mg compared to placebo, and for the higher thresholds, it was also greater than with 2.4 mg. The safety profile of semaglutide was consistent with previous research on GLP-1 receptor agonists. Gastrointestinal adverse events were the most frequently reported, occurring in 70.8% of participants receiving 7.2 mg, 61.2% of those taking 2.4 mg, and 42.8% of the placebo group. The most common reported issues were nausea, diarrhoea, vomiting, and constipation. These events were generally mild to moderate, transient, and mostly occurred during the dose escalation phase. In summary, the STEP-up 3B trial shows that increasing the dose of semaglutide to 7.2 mg results in a clinically meaningful weight reduction compared to the standard 2.4 mg dose, with a predictable and manageable safety profile (Wharton et al., 2025).

The development of tirzepatide is fundamentally based on our understanding of the human incretin system, especially the distinct roles of various hormones produced in the body. Gastric inhibitory polypeptide (GIP) is secreted by K-cells found in the upper gastrointestinal tract, particularly in the duodenum and jejunum. In contrast, glucagon-like peptide-1 (GLP-1) is produced by L-cells located in the distal ileum and colon (Buchan et al., 1978; Eissele et al., 1992). Connections within the neuroendocrine systems that regulate appetite and body weight

have led to the hypothesis that effective pharmacotherapy for obesity requires targeting multiple signalling pathways simultaneously. In 2009, researchers proposed developing peptides capable of dual activation of GLP-1 and glucagon receptors (GLP-1R and GCGR). The rationale was that combining GLP-1-mediated satiety with glucagon-induced increases in energy expenditure could significantly enhance the efficacy of weight reduction(Day et al., 2009). Building on this poly-agonist concept, the integration of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonism emerged as a logical therapeutic strategy for metabolic diseases, given that GLP-1 and GIP together account for the vast majority of the physiological incretin effect. Both GLP-1R and GIPR are expressed on pancreatic β-cells, and their simultaneous activation in the presence of elevated glucose levels profoundly stimulates insulin secretion. Preclinical studies demonstrated that a modified peptide exhibiting dual GIPR and GLP-1R agonism is more effective in reducing body weight and plasma glucose compared to selective GLP-1 receptor agonists. Tirzepatide (LY3298176) is a 39-amino acid linear peptide engineered precisely as a dual agonist of GIPR and GLP-1R. The molecule is acylated with a C20 fatty diacid attached through a hydrophilic linker. This structural modification allows for reversible, non-covalent binding to serum albumin, thereby prolonging systemic exposure and enabling convenient once-weekly dosing (Coskun et al., 2018).

Mechanistic pharmacology studies, complemented by advanced cryo-electron microscopy, have revealed high-resolution structures of tirzepatide in complex with both GIPR and GLP-1R. Similar to native incretin ligands, tirzepatide adopts an α-helical conformation, with its N-terminus deeply inserted into the transmembrane core of each receptor. In the GIPR complex, the N-terminal Tyr residue and additional core interactions provide an affinity comparable to native GIP, despite the lipid modification (B. Sun et al., 2022). In contrast, interactions with GLP-1R are characterised by reduced stabilisation of the N-terminal segment. This "biased" agonism results in altered signalling dynamics and decreased agonist-induced receptor desensitisation, allowing for sustained receptor activation without rapid internalisation (Coskun et al., 2018; B. Sun et al., 2022). Molecular dynamics simulations indicate that the tirzepatide–GIPR complex is more compact and stable compared to the GLP-1R complex.

This unique structural profile and biased signalling translate directly into multi-organ synergistic effects (Coskun et al., 2018). Within the central nervous system (CNS), tirzepatide exhibits a coordinated mechanism by simultaneously activating both receptors in hypothalamic regions critical for energy homeostasis. This results in a more profound suppression of appetite compared to selective GLP-1R agonists, while brain GIPR activation may also modulate tolerance to anorexigenic signals, potentially mitigating nausea (Samms et al., 2020). A fundamental difference determining the drug's metabolic superiority is its direct effect on adipose tissue. Unlike the GLP-1 receptor, the GIP receptor is highly expressed on adipocytes (Campbell & Drucker, 2013). In vivo studies have demonstrated that GIPR activation by tirzepatide promotes healthy lipid sequestration in subcutaneous adipose tissue and improves its insulin sensitivity, thereby preventing lipotoxicity and ectopic fat deposition in organs such as the liver (Campbell & Drucker, 2013; Thomas et al., 2021). This potent action on lipid handling, combined with GLP-1-dependent delayed gastric emptying, creates a comprehensive, multi-systemic mechanism for sustainable weight reduction and metabolic

improvement (Coskun et al., 2018; Dutta et al., 2021; I˙meryüz et al., 1997). The clinical effectiveness of this dual mechanism was clearly demonstrated in the SURPASS program, which provided the first head-to-head evidence against selective GLP-1 receptor (GLP-1R) agonists. A comprehensive Cochrane meta-analysis confirmed that this integrated approach results in better metabolic outcomes compared to traditional monotherapies. In the landmark SURPASS-2 trial, tirzepatide proved to be more effective than semaglutide, leading to a significantly greater reduction in both HbA1c levels and body weight. This establishes a new standard for the pharmacological management of metabolic disorders (Dutta et al., 2021; Frías et al., 2021).

The SURMOUNT-1 study was designed to examine the effects of tirzepatide on patients with obesity. This was a randomized double-blind, phase III study. Eligible participants were adults aged 18 years or older, had at least one weight loss attempt, and had a BMI exceeding 30 (or 27 if it was associated with obesity complications). 2,539 participants were assigned in a 1:1:1:1 ratio to groups taking tirzepatide at the following doses: 5 mg, 10 mg, 15 mg, and placebo. The drug was administered subcutaneously once a week for 72 weeks. Patients received assistance from qualified staff, which included education on how to introduce physical activity and follow a calorie-restricted diet. The primary endpoint, which assessed the effectiveness of the treatment, included a reduction in body weight of 5%, 10%, 15%, 20%, or more at week 72 of the study. The average change in body weight for the 5 mg dose was -15.0%, for the 10 mg dose it was -19.5%, for the 15 mg dose it was -20.9%, and for the placebo group it was 3.1%. Furthermore, efficacy evaluations designed to assess the drug's effectiveness in participants who strictly adhered to the treatment protocol demonstrated a treatment effectiveness of as much as 22.5% in the 15 mg group. 91% of patients taking the highest dose of tirzepatide achieved a clinically significant weight loss of at least 5%, while only 35% of patients from the placebo group achieved this goal. Data for weight loss of more than 25% show that more than one-third of patients (36%) on the 15 mg dose achieved this goal. This was almost unseen in the placebo group (1.5%). All groups which were using tirzepatide had better mean weight loss results than the control group. The study also described changes in patient metabolic parameters. Patients taking tirzepatide were more likely to achieve reductions in waist circumference, blood pressure, fasting insulin and lipid levels. At week 72, 95.3% of patients with prediabetes before the study returned to normoglycemia, compared to 61.9% of those in the placebo group. At the end of the study, body fat percentage was remeasured, and the group taking the dual analogue lost 25.7 percentage points more body fat. Up to 81.8% of study participants taking tirzepatide reported at least one adverse event, compared with 72% in the placebo group. Gastrointestinal symptoms were the most common, transient, and worsened with increasing dose. The percentage of treatment discontinuations due to adverse events was 4.3%, 7.1%, and 6.2% for tirzepatide 5 mg, 10 mg, and 15 mg, respectively, and 2.6% for placebo (Jastreboff et al., 2022).

In the SURMOUNT-2 study, W Timothy Garvey et al., 2023 show the efficacy of tirzepatide in patients with obesity and type 2 diabetes. It was a randomised, double-blind, 72-week phase III trial with a total number of 938 participants aged 18 years or older with BMI ≥27 kg/m² and type 2 diabetes with an HbA1c level of 7–10% were randomized to receive tirzepatide at

dosages of 10 mg, 15 mg, or placebo. The drug was administered as a subcutaneous injection once a week. Treatment began at a dose of 2.5 mg, which was gradually increased every four weeks until the target dose was reached. Simultaneously, all participants received lifestyle support, including a moderate calorie-deficient diet and recommendations for regular physical activity. The primary endpoints included percentage change in body weight from baseline after 72 weeks and the percentage of patients who achieved at least a 5% weight loss. The impact of treatment on glycemic parameters, such as change in HbA1c and fasting glucose, was also assessed. After 72 weeks, the mean weight loss was 12.8% in the 10 mg tirzepatide group and 14.7% in the 15 mg group, compared with a 3.2% weight loss in the placebo group. A weight loss of at least 5% was achieved by 79% of participants in the 10 mg group and 83% in the 15 mg group, respectively, compared with 32% in the placebo group. A greater proportion of patients treated with tirzepatide also achieved greater weight loss, exceeding 10%, 15%, and 20%. Tirzepatide treatment also had a positive impact on glycemic control; for example, mean HbA1c decreased by approximately 2.1 percentage points in both the 10 mg and 15 mg groups, compared with only 0.5% in the placebo group. Consequently, mean HbA1c at 72 weeks was approximately 6.0% in the tirzepatide groups, compared with 7.5% in the placebo group. A greater proportion of patients in the dual agonist groups achieved HbA1c values below 7% and 6.5%. The study also demonstrated improvements in several cardiometabolic parameters, including waist circumference, blood pressure, and lipid profile. The safety profile was similar to that observed in other studies of incretin agonists. The most frequently reported adverse events were gastrointestinal symptoms, such as nausea, diarrhoea, and vomiting, which occurred primarily during the dose titration period and were generally mild to moderate in severity. Treatment discontinuation due to adverse events occurred in 4% of participants in the 10 mg group, 7% in the 15 mg group, and 4% in the placebo group. The incidence of serious adverse events was similar across groups, and the reported deaths were not considered treatment-related (Garvey et al., 2023).

The SURMOUNT-3 study was designed in order to find out how effective tirzepatide is in a population of adults that effectively lost 5% of their initial body weight. 806 participants were enrolled in the 12-week run-in period of the intensive lifestyle intervention, and 579 achieved the goal. This group was qualified for the next phase of the study, in which participants were divided into two groups: one that used 15mg tirzepatide and the other that used a placebo. Patients taking tirzepatide lost 18.4% of their baseline body weight, while those taking a placebo gained an average of 2.5%. The subsequent endpoints (10%, 15%, 20%) were also achieved more frequently by patients treated with tirzepatide. It is worth mentioning that 94% of the treatment group managed to maintain 80% of the initial weight loss, whereas only 43.8% of the placebo group achieved this. This demonstrates that tirzepatide produces a very large and statistically significant reduction in body weight compared to placebo. Additionally, the drug helps maintain the achieved body weight. Moreover, other factors were noted, such as improvements in several cardiometabolic parameters, including reductions in waist circumference, systolic and diastolic blood pressure, diabetic and lipid parameters. Adverse reactions appeared more often in the tirzepatide group. The most common side effects were mild-to-moderate gastrointestinal adverse events that occurred in 87.1% of the study group

compared with 76.7% with placebo, while serious adverse events were infrequent and similar between groups. Treatment discontinuation due to adverse events occurred in 4.3% of participants in the tirzepatide group compared with 2.6% in the placebo group (Wadden et al., 2023).

The SURMOUNT-4 study evaluates the effectiveness of subcutaneous tirzepatide administered once weekly in a study population that also follows calorie deficit and increased physical activity. All participants initially received 36 weeks of tirzepatide treatment, followed by a 52-week double-blind, placebo-controlled period in which patients were randomised either to continue tirzepatide at the maximum tolerated dose or were switched to placebo. The study included adults aged 18 years or older with a body mass index (BMI) of ≥30, or ≥27 in the presence of at least one weight-related complication. Key exclusion criteria were diagnosis of diabetes within the previous three months, obesity, pharmacotherapy that promotes weight loss, and prior or planned bariatric surgery. All participants received standardised lifestyle counselling from healthcare professionals and were advised to follow a reduced-calorie diet with an energy deficit of approximately 500 kcal per day and to engage in at least 150 minutes of physical activity per week. During the initial run-in phase, participants experienced a mean weight reduction of approximately 20.9%. During the subsequent double-blind phase, participants who continued tirzepatide therapy achieved an additional mean body weight reduction of 5.5%, whereas those switched to placebo experienced a mean weight regain of 14.0%. A significantly greater proportion of participants continuing tirzepatide maintained at least 80% of the weight lost during the 36-week run-in period compared with those receiving placebo. These findings demonstrate that continued tirzepatide therapy not only supports the maintenance of previously achieved weight loss but may also promote further weight reduction. Compared with placebo, continued tirzepatide therapy resulted in significant improvements in BMI, glycemic parameters, lipid profile, blood pressure, and several quality-of-life measures between weeks 36 and 88. The most common adverse events reported by study participants were gastrointestinal events. These were more common in the treatment group. Most adverse events were mild to moderate in severity, and their incidence decreased over time during the run-in period with tirzepatide and remained stable during the double-blind phase. Discontinuation due to adverse events during the double-blind period occurred in 1.8% of participants receiving tirzepatide and 0.9% of those receiving placebo (Aronne et al., 2024).

Glucagon is a peptide hormone secreted by pancreatic α-cells that regulates energy metabolism through activation of the glucagon receptor (GCGR), which is expressed primarily in the liver, kidneys, adipose tissue, and the central nervous system, including the arcuate nucleus. Activation of GCGR stimulates catabolic processes, including hepatic glucose production, lipolysis, and fatty-acid oxidation. Although isolated glucagon signalling may elevate blood glucose levels, its combination with GLP-1 and GIP receptor activation in triple agonists provides complementary metabolic effects. In this context, GLP-1 and GIP signalling enhance insulin secretion and improve glycemic control, counterbalancing the hyperglycemic potential of glucagon. Consequently, GCGR activation introduces an additional metabolic mechanism, increased energy expenditure, which, together with appetite suppression and improved insulin secretion, promotes a sustained negative energy balance (Enyew Belay et al., 2024). Early

experimental studies investigating incretin-based therapies suggested that combining multiple metabolic hormone pathways could produce synergistic metabolic benefits. Alessandro Pocai et al. demonstrated that simultaneous activation of the Glucagon-like peptide-1 and Glucagon receptors reduces body weight and improves metabolic parameters in obese mice. The dual agonist decreased food intake while increasing energy expenditure, ultimately reversing obesity in animal models (Pocai et al., 2009). Another study by Victor A. Gault et al. expanded this concept by developing a hybrid peptide capable of activating GLP-1, GIP and glucagon receptors. In high-fat-fed mice, this triple-acting peptide improved glucose tolerance, enhanced insulin secretion, and produced favourable metabolic effects, providing early experimental evidence that simultaneous activation of multiple incretin pathways could improve metabolic efficacy (Gault et al., 2013). Brian Finan et al. reported a monomeric peptide triagonist targeting GLP-1, GIP, and glucagon receptors. In rodent models of obesity and diabetes, this balanced triple agonism resulted in substantial weight loss, improved glycemic control, and reversal of hepatic steatosis, outperforming previously developed mono- and dual-agonist drugs. These discoveries established the pharmacological basis for multi-receptor incretin therapies and ultimately paved the way for the development of modern triple agonists such as Retatrutide (Finan et al., 2015). LY3437943 is a novel triple agonist with balanced activity against GCGR and GLP-1R and the highest activity against GIPR. It is a 39-amino acid peptide designed based on the GIP peptide backbone, whose peptide sequence contains three amino acid residues at positions 2, 13, and 20. The Aib2 (α-amino isobutyric acid) substitution increases the stability of the molecule by resisting degradation by the DPP-4 enzyme, while Aib20 improves the pharmacokinetic profile and activity against the GIP receptor. In turn, α-methyl-L-leucine at position 13 supports optimal activity against glucagon and GIP receptors. The molecule is conjugated to the C20 fatty acid chain by a lysine residue at position 17, enabling reversible binding to albumin and extending the drug's half-life (Coskun et al., 2022). These experimental discoveries led to the invention of retatrutide, a synthetic incretin-based peptide designed to function as a triple agonist of the GLP-1, GIP and glucagon receptors. Retatrutide combines appetite suppression with increased energy expenditure and improves insulin secretion. This innovation represents the next generation of multi-receptor incretin therapies for obesity and metabolic diseases (Li et al., 2024; Melson et al., 2025).

The efficacy and safety of retatrutide in obesity were evaluated in a phase 2, multicenter, randomised, double-blind, placebo-controlled trial published in The New England Journal of Medicine and led by Ania M. Jastreboff. The study assessed the effects of once-weekly subcutaneous administration of retatrutide on body-weight reduction in a group of 338 adults aged 18–75 years with a BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related comorbidity. Participants were randomly assigned in a 2:1:1:1:1:2:2 ratio to receive retatrutide at doses of 1 mg, 4 mg, 8 mg, or 12 mg, or placebo for 48 weeks, followed by a 4-week safety follow-up period. For doses ≥4 mg, to improve tolerability, the dose was gradually increased every 4 weeks for up to 12 weeks. All participants received a healthcare professional consultation regarding lifestyle changes. Key exclusion criteria included a diagnosis of diabetes, previous or planned bariatric surgery, use of pharmacological weight-loss or weight-gain therapy, and a body-weight change of more than 5 kg within 3 months before screening.

The primary endpoint was the percentage change in body weight at 24 weeks. Weight reduction was significantly greater in the retatrutide groups than in the placebo group. Participants taking 1 mg of retatrutide lost 7.2% of their body weight, while those taking 12 mg of the drug lost as much as 17.5% of their body weight. For comparison, in the placebo group, the weight loss was only 1.6%. Similar results were observed at week 48. Additional secondary outcomes showed that from 64 to 100% of participants receiving retatrutide achieved ≥5% weight loss, compared with 27% in the placebo group. Weight loss of 20% or more was more common in participants who received at least 4 mg of retatrutide than in those who received a placebo. The study also showed that the use of retatrutide was associated with improvements in several cardiometabolic parameters, including reductions in blood pressure and improvements in glycemic markers such as glycated haemoglobin, fasting glucose, and insulin levels at both 24 and 48 weeks. Favourable changes were also observed in lipid profiles, although HDL cholesterol levels remained largely unchanged. Among participants with prediabetes at baseline, 72% of those receiving retatrutide returned to normoglycemia after 48 weeks, compared with 22% in the placebo group. The overall safety profile of retatrutide was comparable to placebo. Serious adverse events occurred in 4% of participants in both the retatrutide and placebo groups. Most reported adverse events were gastrointestinal and generally mild to moderate in severity. Transient elevations in liver enzymes were rare (approximately 1% of participants) and typically resolved without clinical consequences. Increases in pancreatic enzyme levels were mostly asymptomatic, with one reported case of acute pancreatitis. Up to week 24, an increase in heart rate was observed in a dose-dependent manner with retatrutide; the measured values then decreased (Jastreboff et al., 2023).

A subsequent substudy conducted by Sanyal et al. evaluated the effects of retatrutide on metabolic dysfunction-associated steatotic liver disease (MASLD) in a subgroup of participants from the phase 2 obesity trial reported by Jastreboff et al. This analysis included 98 participants, all of whom had at least 10% hepatic fat content measured by magnetic resonance imaging with proton density fat fraction (MRI-PDFF). A total of 338 individuals were taking part in the main study. The participants were randomly assigned to receive either a placebo or retatrutide, administered once weekly at doses of 1 mg, 4 mg, 8 mg, or 12 mg. Retatrutide treatment resulted in substantial reductions in liver fat content. After 24 weeks of therapy, the relative reduction in hepatic fat was significantly greater for all retatrutide doses compared with placebo. Mean reductions from baseline reached −42.9%, −57.0%, −81.4%, and −82.4% for the 1 mg, 4 mg, 8 mg, and 12 mg doses, respectively, while the placebo group showed no meaningful change. The assessed parameters were also examined at 48 weeks, with relative reductions ranging from −51.3% to −86.0% in the retatrutide groups compared with −4.6% in the placebo group. A notable proportion of participants receiving retatrutide achieved clinically relevant reductions in hepatic fat. 71–100% of individuals reached at least a 30% reduction after 24 weeks. Normalisation of liver fat content (<5%) was achieved in up to 79% and 86% of participants receiving the 8 mg and 12 mg doses of triple agonist at week 24, increasing to 89% and 93% by week 48. Retatrutide treatment led to reductions in hepatic steatosis, liver volume, and abdominal fat (both visceral and subcutaneous) in a dose-dependent manner. The reduction in hepatic fat correlated strongly with decreases in body weight and

waist circumference, suggesting that improvements in liver steatosis are closely linked to the metabolic effects of the triple-receptor agonist. Retatrutide treatment was associated with favourable changes in several biomarkers related to steatohepatitis and fibrogenesis. Significant decreases were observed in circulating cytokeratin-18 (K-18), a marker of hepatocyte apoptosis. After 48 weeks of treatment, reductions in K-18 reached approximately 49.6% in the 8 mg retatrutide group compared with a 28.0% reduction in the placebo group, suggesting a substantial decrease in hepatocellular injury. The safety profile observed in this substudy was consistent with that reported in the main obesity trial. Gastrointestinal symptoms were the most frequently reported adverse events and were generally mild to moderate in severity. No signals of hepatotoxicity were detected during the 48-week treatment period (Sanyal et al., 2024).

The efficacy and safety of retatrutide in patients with type 2 diabetes were evaluated in a phase 2, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group trial conducted in the United States. The study included adults aged 18–75 years with type 2 diabetes and glycated hemoglobin (HbA1c) levels between 7.0% and 10.5%, who were treated with lifestyle modification alone or a stable dose of metformin (≥1000 mg daily) for at least 3 months before screening. Participants were also required to have a body mass index between 25 and 50 kg/m² and a stable body weight (±5 kg) during the 3 months preceding randomization. A total of 281 participants were randomly assigned in a 2:2:2:1:1:1:1:2 ratio to receive placebo, dulaglutide 1.5 mg, or retatrutide at maintenance doses of 0.5 mg, 4 mg, 8 mg, or 12 mg with different dose-escalation regimens. To maintain masking, a double-dummy design was used, in which participants received two weekly injections consisting of an active drug and a matched placebo. The trial included a 3-week screening period, followed by a 36-week treatment phase and a 4-week safety follow-up. Retatrutide treatment resulted in substantial reductions in HbA1c levels compared with placebo. At week 24, the least-squares mean reduction in HbA1c ranged from -0.43% with the 0.5 mg dose to -2.02% in the 12 mg escalation group. The reduction in HbA1c was greater in all retatrutide groups compared with placebo and exceeded that observed with the GLP-1 receptor agonist dulaglutide in the 8 mg slow-escalation and 12 mg groups. Similar results were observed in the data from week 36, where the largest decrease in HbA1c was recorded in the 12 mg group, showing a reduction of -2.16%. These findings illustrate a clear dose-dependent improvement in glycemic control with retatrutide in patients with type 2 diabetes. Another evaluated parameter was fasting serum glucose levels after 36 weeks of treatment. The mean change from baseline ranged from -17.26 mg/dL in the 0.5 mg group to -67.84 mg/dL in the 12 mg escalation group. Greater reductions were observed at higher doses, including -38.72 mg/dL in the 4 mg group and -69.10 mg/dL in the 8 mg slow-escalation group, indicating a clear dose-dependent effect. Compared with placebo, the reduction in fasting glucose was greater in the retatrutide groups, and the glucose-lowering effect of the higher retatrutide dose exceeded that observed in the 1.5 mg dulaglutide groups, particularly in the 8 mg slow-escalation and 12 mg groups, indicating the potent metabolic activity of the triple agonist. The weight change from baseline was assessed at week 36. Weight loss was greater in all retatrutide groups than in the control group. The mean reduction ranged from -3.31 kg in the 0.5 mg group to -17.18 kg in the 12 mg escalation group,

whereas the placebo group showed a reduction of -3.28 kg. The triple agonist was also more effective than the GLP-1 agonist (Rosenstock et al., 2023).

4. Comparative metabolic efficacy of incretin polyagonists

To enable comparisons across different trials, we selected the highest studied therapeutic doses for each medication. This analysis focuses on the comparative metabolic efficacy of incretin monoagonists and polyagonists. Lipid outcomes reported as estimated treatment ratios in STEP trials were converted to percentage change from baseline using the formula (ratio - 1) × 100 to allow cross-trial comparison. Although these findings suggest superior efficacy of multi-receptor agonists, direct comparisons between studies should be interpreted with caution due to differences in trial design, study populations, and treatment duration.

Table 1. Summary of clinical efficacy and metabolic outcomes associated with semaglutide, tirzepatide, and retatrutide in randomised clinical trials.

Parameter	STEP program - Semaglutide 2.4mg (68 to 72 weeks)	SURMOUNT program –Tirzepatyd 15mg (72 weeks)	Phase II trial – Retatrutide 12 mg (48 weeks)	Phase II trial – Retatrutide 12mg (36 weeks)
Receptor targets	GLP-1	GLP-1 + GIP	GLP-1 + GIP + GCGR	GLP-1 + GIP + GCGR
Mean weight loss (%)	(9.6 - 16.0)	(14.7 to 20.9)	24.2	16.94
Patients ≥5% weight loss (%)	(68.8 to 89.9)	(83.0 to 90.9)	100	94
Patients ≥10% weight loss (%)	(45.6 to 75.3)	(65.0 to 83.5)	93	71
Patients ≥15% weight loss (%)	(25.8 to 55.8)	(48.0 to 70.6)	83	58
Patients ≥ 20% weight loss (%)	(13.1 to 35.7)	(31.0 to 56.7)	64	40
Change in waist circumference (cm)	(9.4 to 14.6)	(13.1 to 18.5)	19.5	13.24
HbA1c reduction (percentage points)	(-1.6 to -0.3)	(-2.08 to -0.51)	-0.4	-2.16
Fasting glucose change (mg/dl)	(-37.8 to -6.73)	(-48.9 to -10.6	-10.6	-67.84
Total cholesterol (change %)	(-5 to -1)	(-7.4 to -2.2)	-17.8	-14.83
Triglycerides (change %)	(-22 to -16)	(-31.4 to -30.6)	-39.9	-34.35
VLDL cholesterol (change %)	(-22 to -15)	(-31.7 to -29.5)	-38.8	-33.76
LDL cholesterol (change %)	(-7 to 0)	(-8.6 to 3.2)	-21.7	-6.87
HDL cholesterol (change %)	(5 to 7)	(8.2 to 9.6)	2.5	-1.68

Systolic blood pressure (mmHg)	(-8.7 to -3.9)	(-7.7 to -7.2)	-11.0	-8.79
Diastolic blood pressure (mmHg)	(-3 to -1.6)	(-4.8 to -2.9)	-5.1	-3.89
Adverse events (% of population)	(84.1 to 95.8)	(71.0 to 78.9)	92	76
Adverse events leading to treatment discontinuation (% of population)	(4.0 to 7.0)	(6.2 to 7.0)	16	15

5. Discussion:

A comparison analysis of clinical trial outcomes shows that weight reduction and metabolic parameters improve progressively with more complex receptor interactions. Although this observation is currently based on phase II data retatrutide demonstrated the greatest magnitude of weight reduction among the analysed therapies, with a mean weight loss of 24.2% during a 48-week trial, exceeding the effects observed with tirzepatide and semaglutide. The proportion of patients achieving clinically significant weight loss thresholds (≥10%, ≥15%, and ≥20%) was highest in the triple agonist group. Beyond weight reduction, all agents showed metabolic effects, including improvements in glycemic control, lipid profile, and blood pressure; the values of metabolic improvements increased with the number of targeted receptors. The incidence of adverse events remained high across all treatment groups and appeared to increase with a greater number of receptor activations and higher dosing, leading to treatment discontinuation more frequently. Gastrointestinal symptoms represented the most frequently reported adverse events and were the main reason for treatment discontinuation.

In clinical trials, study groups often received different doses of medications. The trend of higher doses leading to more favourable metabolic outcomes was consistent across all studies of each drug. In the STEP UP phase 3b trial, a 7.2mg dose of semaglutide was compared with a 2.4mg dose. The results of this study indicate a greater average weight loss (18.7% vs. 15.6%). A significantly greater percentage of participants achieved a 25% weight loss in the higher-dose group (31.2% vs 15.3%) (Wharton et al., 2025). Supportive secondary endpoints were also more favourable in this group. A similar relationship between dose and metabolic response was observed in the SURMOUNT-1 trial. The percentage weight loss was greater with the higher dose of tirzepatide. For the 5mg dose, the percentage was 15.0%; for the 10mg dose, it was 19.5%; and for the 15mg dose, it was 20.9%. Patients on the 15mg dose also achieved a weight loss of 20% or more most frequently (56.7%), while for the 5mg and 10mg doses, the results were 30.0% and 50.1%, respectively (Coskun et al., 2022). Results from the phase 2 retatrutide study by Ania M. Jastreboff et al. also show that higher doses of retatrutide can achieve better

results than lower doses. Participants receiving 12mg of retatrutide achieved the greatest percentage weight loss (23.9%) at week 48 of the study, while those receiving the 8mg dose lost 21.7%. Participants receiving the 12mg dose also achieved the best secondary endpoints (Jastreboff et al., 2023). In the studies we reviewed, the most commonly reported adverse events were gastrointestinal symptoms such as nausea, vomiting, diarrhoea, constipation, and dyspepsia. Less frequent adverse events included arrhythmias and local allergic reactions. Adverse events occurred more often at higher doses, and their severity significantly increased during the dose escalation period. Most side effects were classified as mild to moderate; severe adverse events were more likely to occur at higher doses. Participants in the groups receiving the maximum tested dose of the drug discontinued treatment more frequently than those in groups receiving lower doses.

The STEP-1 and SURMOUNT-4 extension studies demonstrate the nature of obesity and its chronic nature. Receiving Semaglutide resulted in an initial average weight loss of 17.3% this change was not maintained, and participants gained 11.6 percentage points of lost weight. Metabolic parameters, such as lipids and cardiovascular parameters, also worsened at week 120 if we compare them to results from week 68. The Surmount-4 study also demonstrated the difficulty in maintaining the effects of 36 weeks of tirzepatide treatment. Participants who received a placebo after this period regained 14.0% of their weight, while the group who continued receiving tirzepatide lost an additional 5.5%. These results may indicate that obesity is a chronic disease that requires ongoing treatment, similar to hypertension or diabetes (Coskun et al., 2022; Wilding et al., 2022).

The weight loss results achieved with retatrutide can also be compared with those following bariatric surgery. This comparison should be interpreted with caution due to differences in follow-up duration between pharmacological trials and surgical studies. In a study by Anita P. Courcoulas, MD, MPH, et al., which assessed the percentage weight loss three years after Roux-en-Y gastric bypass (RYGB) or laparoscopic adjustable gastric banding (LAGB), the percentage weight loss compared to baseline was 31.5% for RYGB and 15.9% for LAGB. When comparing these values to the percentage weight loss achieved with retatrutide after 48 weeks (24.2%), the results indicate that bariatric surgery remains the most effective method for weight loss. However, weight loss observed with the new triple agonist approaches the lower range of outcomes typically achieved with bariatric surgery (Courcoulas, 2013).

6. Limitations

The primary constraints are the absence of head-to-head studies, which could provide direct comparisons of the effectiveness of these three medications in the same patient population. Some studies focused on individuals with diabetes, while other studies specifically excluded this disease. The differing lengths of the studies, which included treatment durations of 36, 48, 68, and 72 weeks, imply that the outcomes might have varied if the studies had been conducted over the same time period. Nonetheless, the specific durations of certain studies (the more receptors activated, the shorter period of time study lasted), along with the clinical aspect (where primary and secondary treatment objectives were met with better outcomes using the

triple agonist despite a shorter duration), raise concerns that multireceptor therapy could be the most effective treatment alternative and suggest an increased demand for this medication among patients. Retatrutide is presently undergoing Phase III clinical trials, and there are no available data from this phase to elaborate further on the issues being examined. Additionally, as a narrative review, this study is subject to potential selection bias and does not follow a systematic methodology for study inclusion.

7. Conclusion

Obesity remains a major global health challenge associated with numerous metabolic and cardiovascular complications. Incretin-based therapies have emerged as an effective pharmacological strategy for weight reduction and metabolic improvement. Clinical trials show that therapies targeting multiple receptors, such as tirzepatide and retatrutide, lead to greater weight loss and increase metabolic benefits compared to single-receptor agonists. In particular, phase II clinical trials of the triple agonist retatrutide have shown the greatest magnitude of weight reduction among currently investigated pharmacological therapies. Although bariatric surgery remains the most effective intervention for severe obesity, the weight loss achieved with triple receptor agonist approaches the lower range of surgical outcomes. Ongoing phase III clinical trials will further clarify the long-term efficacy and safety of these therapies and their potential role in the future management of obesity.

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