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NEW ERA IN OBESITY TREATMENT: EFFECTS OF GLP-1 AGONISTS, DUALS (GIP) AND TRIPLES (GLUCAGON) ON DIABETES MELLITUS, OBESITY, AND OTHER SYSTEMIC OUTCOMES – INTEGRATIVE REVIEW

Danilo Gustavo Gonçalves Ferreira Romanelli [1], Ana Cristina Faria Silva Romanelli[2]

Corresponding E-mail: daniloromanelli@yahoo.com.br
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ABSTRACT

Objective: To analyze the effects of GLP-1 receptor agonists, dual GIP/GLP-1 agonists, and triple GIP/GLP-1/glucagon agonists on reducing body weight, controlling type 2 diabetes mellitus, and the main systemic outcomes associated with obesity. **Methods:** An integrative literature review was conducted, with searches in PubMed/MEDLINE and additional tracking in the Scopus, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov. The primary studies published between January 2015 and July 2026 were included, involving adults with obesity, overweight, type 2 diabetes, or complications related to adiposity. Phase II and III randomized clinical trials, cardiovascular and renal outcomes studies, long-term extensions, and clinical substudies were prioritized. The final sample comprised 35 studies: 17 on liraglutide or semaglutide, 14 on tirzepatide, and four on retatrutide. **Results:** Liraglutide produced average weight losses of approximately 6% to 8%, while semaglutide 2.4 mg achieved reductions close to 15% in individuals without diabetes. Tirzepatide produced losses of more than 20% in people with obesity without diabetes, along with significant reductions in glycated hemoglobin in patients with type 2 diabetes. Retatrutide showed weight loss of up to 24.2% in a phase II study and confirmed high glycemic and weight-lowering efficacy in a phase III trial. Semaglutide demonstrated reductions in cardiovascular and renal events, as well as benefits in heart failure, osteoarthritis, and metabolic-associated liver disease. Tirzepatide showed favorable effects on heart failure, obstructive sleep apnea, steatohepatitis, and prevention of progression of prediabetes. The most frequent adverse events were gastrointestinal, mainly during dose escalation. Discontinuation studies demonstrated significant weight regain after stopping treatment. **Conclusion:** The evolution from isolated GLP-1 agonism to dual and triple strategies substantially expanded the effectiveness of obesity pharmacotherapy. Semaglutide and tirzepatide have consistent evidence on metabolic and systemic outcomes, while retatrutide represents a promising alternative, still dependent on continued safety confirmation and cardiovascular and renal benefit in the long term. Treatment should be individualized, ongoing, and combined with nutritional, behavioral, and functional interventions.

Keywords: Obesity; GLP-1 Receptor Agonists; Type 2 Diabetes Mellitus; Weight Loss; Cardiometabolic Diseases.

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INTRODUCTION

Obesity is a chronic, progressive, relapsing disease of multifactorial etiology, characterized by the excessive accumulation of adipose tissue and by neuroendocrine and metabolic alterations. inflammatory and Behavioral factors that hinder the maintenance of weight loss. Their clinical relevance goes beyond simply increasing body mass index, since adiposity... Excessive obesity directly contributes to the pathophysiology of type 2 diabetes mellitus, hypertension, dyslipidemia, atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, fatty liver disease associated with metabolic dysfunction, obstructive sleep apnea, and osteoarticular limitations. In this context, obesity treatment should be understood as an intervention aimed not only at reducing body weight, but also at modifying cardiometabolic risk and preventing systemic complications.

For decades, therapeutic strategies to obesity Treatments remained focused on caloric restriction, increased physical activity, and behavioral interventions. While these measures are indispensable, the isolated response is often limited by the activation of compensatory mechanisms, such as increased hunger, reduced satiety, decreased energy expenditure, and metabolic adaptation. These physiological responses favor the recovery of lost weight and partly explain the high recurrence rate after exclusively behavioral interventions. The introduction of liraglutide at a dose of 3.0 mg represented an initial milestone in modern pharmacotherapy for obesity, demonstrating that modulation of the glucagon-like peptide-l receptor, or GLP-l, could produce clinically relevant weight loss and improve parameters. glycemic and cardiometabolic effects in people with and without type 2 diabetes (l,2). Furthermore, the benefits observed in individuals with obesity and obstructive sleep apnea indicated that pharmacological reduction of adiposity could have an impact on respiratory complications associated with excess weight (3).

GLP-l is an incretin hormone secreted primarily by intestinal enteroendocrine cells in response to nutrient intake. Its activation promotes glucose-dependent insulin secretion, reduces glucagon release, delays gastric emptying, and centrally modulates appetite and

satiety. These properties have made GLP-1 receptor agonists important agents for the treatment of type 2 diabetes and, subsequently, obesity. However, the relevance of this class has not remained restricted to glycemic control and weight reduction. The LEADER study demonstrated that liraglutide reduced major cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and high cardiovascular risk (4). Similarly, SUSTAIN-6 identified a reduction in cardiovascular events with subcutaneous semaglutide, in addition to favorable signals on renal outcomes, consolidating the hypothesis that GLP-1 agonism could exert additional vascular, renal, inflammatory, and metabolic effects (5).

Semaglutide at a weekly dose of 2.4 mg substantially increased the pharmacological efficacy observed in the treatment of obesity. In the STEP program, therapy promoted an average weight loss close to 15% in adults without diabetes and significant reductions, although generally smaller, in patients with type 2 diabetes (6,7) . Maintenance studies showed that ongoing therapy is fundamental to preserving weight loss, while stopping the medication is associated with a significant recovery of weight, reinforcing obesity's chronic, relapsing nature (8) . Semaglutide also demonstrated effects on conditions directly related to adiposity, including metabolic steatohepatitis, in which it increased the frequency of resolution of hepatic inflammatory activity, although there was no initial conclusive evidence of fibrosis regression (9) . Direct comparisons showed the superior weight outcome of weekly semaglutide over daily liraglutide, indicating the progression of efficacy within the GLP-1 agonist class itself (10) . Maintaining results for up to two years confirmed that the response could be sustained during continued treatment (11) .

The clinical impact of semaglutide became even more relevant when its benefits were demonstrated across systemic and cardiovascular outcomes. The SELECT study showed a reduction in major cardiovascular events in individuals with overweight or obesity, established cardiovascular disease, and no diabetes, providing one of the first demonstrations that pharmacological treatment of obesity could modify cardiovascular pr-

ognosis independently of a diagnosis of type 2 diabetes (12). In patients with heart failure with preserved ejection fraction and obesity, with or without diabetes, semaglutide improved symptoms, functional capacity, quality of life, and inflammatory parameters (13, 14). The FLOW study added evidence of renal protection by showing reduced progression of chronic kidney disease and cardiovascular events in patients with type 2 diabetes (15). In addition, improved pain and physical function in people with obesity and knee osteoarthritis expanded the range of benefits to musculoskeletal and functional outcomes (16).More recently, the oral formulation of semaglutide also demonstrated a reduction in cardiovascular events in patients with high-risk type 2 diabetes, indicating that the molecule's cardioprotection is not restricted to the subcutaneous route (17).

Despite the advances achieved with GLP-1 receptor agonists, the search for greater glycemic and weight effectiveness drove the development of molecules capable of simultaneously activating different hormone receptors. Tirzepatide, a dual agonist of the glucose-dependent insulinotropic polypeptide receptor, or GIP, and GLP-1, ushered in a new era of incretin-based therapy. In the SURPASS studies, the drug promoted marked reductions in glycated hemoglobin and body weight across different stages of type 2 diabetes, including patients treated with nonpharmacological measures alone, metformin, basal insulin, or more complex treatment regimens (18-21). In direct comparison, tirzepatide demonstrated greater glycemic and weight reduction than semaglutide 1.0 mg in individuals with type 2 diabetes, although this comparison did not involve the 2.4 mg dose used specifically for obesity (19).

In the SURMOUNT studies, tirzepatide produced an average weight loss of more than 20% in adults with obesity without diabetes, bringing pharmacotherapy to magnitudes traditionally associated to more invasive metabolic interventions (22). In people with obesity and type 2 diabetes, weight reduction was smaller, but it remained clinically significant and accompanied by a substantial improvement in glycemic control (23). The association with intensive lifestyle intervention increased weight loss, showing that pharmacotherapy can act as a complem-

ent to behavioral strategies (24). However, withdrawal studies showed an important regain of weight after discontinuation, reinforcing that efficacy depends on ongoing treatment and that obesity should not be addressed as a condition for temporary therapy (25).

Tirzepatide also showed relevant effects on systemic obesity-related complications. In patients with obstructive sleep apnea, it significantly reduced the apnea-hypopnea index, hypoxic burden, body weight, and cardiometabolic markers (26) . In individuals with steatohepatitis associated with metabolic dysfunction and fibrosis, it increased the resolution of inflammatory liver disease and showed favorable signs regarding fibrosis regression (27) . In the SUMMIT study, it reduced worsening events of heart failure in patients with obesity and preserved ejection fraction, and also improved symptoms and quality of life (28) . Prolonged follow-up of individuals with prediabetes indicated a substantial reduction in progression to type 2 diabetes during treatment, suggesting a preventive potential associated with sustained weight loss and improvement in glycemic physiology (29) . Compared directly with semaglutide 2.4 mg, tirzepatide resulted in greater average weight loss, although both therapies showed clinically relevant benefits (30) .In the cardiovascular field, the SURPASSCVOT study demonstrated noninferiority of tirzepatide compared with dulaglutide, but did not confirm statistical superiority over this GLP-1 agonist with previously established cardiovascular benefit (31) .

The most recent development in incretin pharmacotherapy involves molecules with simultaneous action on three metabolic receptors. Retatrutide combines agonism of the GIP, GLP-1, and glucagon receptors, aiming to integrate appetite reduction, improved secretion and insulin sensitivity, glucagon modulation, and increased energy expenditure. In a phase II study with individuals with obesity, the molecule produced average weight reductions of more than 20%, with a dose-dependent response and no clear weight plateau at the end of follow-up (32). In patients with type 2 diabetes, it also yielded substantial reductions in glycated hemoglobin and body weight (33). Results in metabolic steatotic liver disease showed a marked decrease in hepatic fat content,

suggesting a potential effect on hepatic and visceral lipid metabolism (34). Publication of the first phase III trial confirmed high glycemic and weight efficacy in people with type 2 diabetes, although broader evidence is still needed regarding long-term safety, cardiovascular events, renal outcomes, and direct comparison with semaglutide and tirzepatide (35).

Despite the consistency of the results, the comparative interpretation between isolated, dual, and triple agonists requires caution. The trials differ regarding the presence of diabetes, severity of obesity, length of follow-up, dose used, comparators, intensity of the behavioral intervention, and statistical treatment methods for missing data. Superiority in weight reduction does not necessarily imply superiority in mortality, cardiovascular events, renal protection, or long-term safety. In addition, the frequency of events gastrointestinal, the discontinuations, the possible effects on the gallbladder, heart rate, body composition, and weight regain after withdrawal remain central aspects for clinical decision-making.

Given this scenario, an integrated synthesis of the available evidence is necessary to understand the transition from isolated GLP-l agonism to double GIP/GLP-l agonism and triple GIP/GLP-l/glucagon agonism strategies. Thus, this integrative review aimed to analyze the effects of these therapies on reducing body weight, controlling type 2 diabetes mellitus, and the main systemic outcomes, including cardiovascular, renal, hepatic, respiratory, functional, and osteoarticular repercussions, as well as to discuss their limitations, safety, the need for continuity, and perspectives for contemporary obesity treatment.

METHODOLOGY

The present study was characterized as an integrative literature review, with a qualitative approach and a purpose descriptive-analytical,
developed with the purpose of critically synthesizing the available evidence on the effects of GLP-l receptor agonists, double agonists of the GIP/GLP-l receptors, and triple agonists of the GIP/GLP-l/glucagon receptors in the treatment of obesity, in the control of type 2 diabetes

mellitus, and in associated systemic outcomes. The integrative review was chosen because it makes it possible to bring together and compare studies with different populations, interventions, comparators, and clinical outcomes, thereby enabling a comprehensive understanding of the evolution of incretin pharmacotherapy and its repercussions metabolic, cardiovascular, renal, hepatic, respiratory, functional, and osteoarticular.

The review was prepared using the following steps: defining the guiding question; establishing eligibility criteria; building the search strategy; identifying and selecting the studies; standardized extraction of information; critical appraisal of methodological quality; organizing the findings by pharmacological classes and outcomes; and interpretive synthesis of the evidence. The guiding question was formulated in the following terms: what are the effects of isolated GLP-1 receptor agonists, dual GIP/GLP-1 agonists, and triple GIP/GLP-1/glucagon agonists on reducing body weight, glycemic control, and systemic outcomes in adults with obesity, overweight, type 2 diabetes mellitus, or complications related to adiposity?

The research question structure considered the PICOS strategy components. The population consisted of adults aged 18 years or older, with obesity, overweight associated with comorbidities, type 2 diabetes mellitus, or systemic conditions related to excess adiposity. The interventions understood liraglutide, semaglutide, tirzepatide, and retatrutide, administered at the doses and regimens evaluated in their respective clinical trials. The comparators included placebo, lifestyle intervention, insulin glargine, dulaglutide, liraglutide, semaglutide, or other active treatments used in the original studies. Outcomes of interest included absolute and relative changes in body weight, the proportion of participants who achieved losses weight clinically relevant, change in glycated hemoglobin, control of type 2 diabetes, progression from prediabetes to diabetes, major cardiovascular events, mortality, heart failure, progression of chronic kidney disease, metabolic-associated liver disease, obstructive sleep apnea, osteoarthritis, functional capacity, quality of

life, and safety. Regarding the design, randomized phase II and III clinical trials, cardiovascular and renal outcomes studies, randomized extensions, and previously specified clinical substudies were prioritized.

The bibliographic search was conducted during July 2026, with a final update on 23 July 2026. The main search was carried out in PubMed/MEDLINE and supplemented by tracking records in recognized scientific databases and platforms, including Scopus, Web of Science, Embase, Cochrane Library and ClinicalTrials.gov, as well as checking metadata on the official pages of the journals responsible for the publications. A manual search was also performed in the reference lists of the studies considered central, especially in the SCALE, LEADER, SUSTAIN, STEP, SELECT, FLOW, SURPASS, SURMOUNT, SUMMIT, and TRANSCEND clinical programs, with the aim of identifying potentially relevant primary publications and reducing the risk of omitting key trials.

The search strategy combined controlled descriptors and free-text terms related to obesity, type 2 diabetes, the investigational drugs, and the main systemic outcomes. The terms in English **"**obesity**"**, **"**overweight**"**, **"**type 2 diabetes mellitus**"**, **"**weight loss**"**, **"**body weight**"**, **"**GLP-1 receptor agonist**"**, **"**glucagon-like peptide-1 receptor agonist**"**, **"**liraglutide**"**, **"**semaglutide**"**,**"**dual GIP/GLP-1 receptor agonist**"**,**"**tirzepatide**"**, **"**triple GIP/GLP-1/glucagon receptor agonist**"**, "retatrutide", "cardiovascular outcomes", "major adverse cardiovascular events", "heart failure", "chronic kidney disease", "renal outcomes", "metabolic dysfunction-associated steatotic liver disease**"**, **"**metabolic dysfunctionassociated steatohepatitis**"**, **"**obstructive sleep apnea**"**, **"**osteoarthritis**"**, **"**glycemic control**"**, and **"**diabetes prevention**"**. The Boolean operators **"**AND**"** and **"**OR**"** were used to combine terms related to the population, intervention, and outcomes. The search focused on studies published between January 2015 and July 2026, a time window corresponding to the clinical consolidation of liraglutide at an anti-obesity dose and the subsequent development of semaglutide, tirzepatide, and retatrutide.

Eligible articles were considered original published

fully in peer-reviewed scientific journals that assessed adult human beings and reported primary efficacy, safety, or systemic outcome results related to GLP-1, GIP/GLP-1, or GIP/GLP-1/glucagon agonists. Studies were included with participants with or without type 2 diabetes, provided they presented obesity, overweight with comorbidity, or a clinical condition directly related to adiposity. Cardiovascular and renal trials were included even when weight loss was not the primary endpoint, due to their relevance for assessing the ability of these therapies to modify systemic prognosis. Trial extensions and substudies were accepted when they reported distinct and clinically relevant outcomes, such as prevention of diabetes, maintenance of weight loss, liver fat, fibrosis, heart failure, sleep apnea, or osteoarthritis.

Preclinical studies, experiments with animals or cell cultures, case reports and case series, observational studies without a comparison group, narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, letters to the editor, protocols with no published results, conference abstracts without a full article, pediatric studies, and publications that did not present a direct link to the defined outcomes were excluded. Exclusions were also made secondary redundant from the same population when they did not add a specific outcome to the review. In cases of multiple publications derived from the same clinical program, the main article was selected

and only the extensions or analyses that provided original and relevant results for understanding the treatment over time or across multiple systems were kept.

The selection was conducted in two stages. Initially, the retrieved titles and abstracts were reviewed to verify thematic relevance and alignment with the eligibility criteria. Subsequently, potentially relevant articles were assessed in full text. Duplicates, secondary publications without additional results, and studies that did not meet the predefined population, intervention, comparator, or outcomes were removed. After screening and comprehensive assessment, 35 primary, real, and traceable studies were selected, which formed the final basis of the review. The sample consisted of 17 studies related to GLP-1 receptor agonis-

ts, 14 studies on the dual GIP/GLP-1 agonist tirzepatide, and four studies on the triple GIP/GLP-1/glucagon agonist retatrutide.

Data extraction was carried out using a standardized instrument developed specifically for this review. Authors, year of publication, clinical trial identification, study design, development phase, number of participants, population characteristics, presence or absence of type 2 diabetes, intervention, dose, administration frequency, treatment duration, comparator, primary and secondary outcomes, magnitude of weight loss, change in glycated hemoglobin, proportion of participants who achieved weight-reduction targets, cardiovascular, renal, hepatic, respiratory, functional, and osteoarticular results, adverse events, discontinuations, limitations, and clinical relevance. When available, measures of effect were extracted, such as mean differences, hazard ratios, relative risks, confidence intervals, and levels of statistical significance.

Critical appraisal of the studies considered the main methodological domains applicable to the trials randomized clinical trials, including adequacy of the randomization sequence generation, allocation concealment, blinding of participants, researchers, and assessors, balance between groups, losses during follow-up, adherence, handling of missing data, validity of measurement instruments, consistency between outcomes previously defined and those reported, in addition to the possibility of selective reporting. This assessment was guided by the domains of the Cochrane Risk of Bias 2 tool, without automatically excluding studies with moderate limitations, since the integrative review also seeks to identify weaknesses, discrepancies, and gaps in the body of evidence. Open-label trials, withdrawal studies, and substudies were interpreted considering the specific risks of selection, performance, sample enrichment, and reduced external validity.

The results were initially organized according to the pharmacological mechanism: isolated GLP-1 receptor agonists, represented by liraglutide and semaglutide; dual GIP/GLP-1 agonist, represented by tirzepatide; and triple GIP/GLP-1/glucagon agonist, represented by retatrutide. The findings were then grouped by them-

atic axes, including weight-based efficacy, glycemic control, prevention of type 2 diabetes, cardiovascular outcomes, heart failure, chronic kidney disease, metabolic-associated liver disease, obstructive sleep apnea, osteoarthritis, weight-loss maintenance, and safety.

Due to the clinical and methodological heterogeneity among the studies, especially regarding populations, doses, comparators, follow-up duration, statistical estimands, and the definition of outcomes, no meta-analysis was performed. The results were synthesized in a narrative and comparative manner, respecting the estimates presented in each original publication. Indirect comparisons indirect between

medicines were interpreted with caution, and a greater weighted reduction was not automatically considered equivalent to greater cardiovascular, renal, or mortality benefit. Randomized direct comparisons, such as semaglutide versus liraglutide, tirzepatide versus semaglutide, and tirzepatide versus dulaglutide, received greater interpretive weight than comparisons between independent trials.

Because it used exclusively secondary data available in publicly or institutionally accessible scientific publications, with no direct contact with participants and without using individually identifiable information, the study did not require submission to an Ethics Committee for Research. The principles of scientific integrity, traceability of sources, fidelity to the original results, and transparency in the interpretation of evidence were respected.

RESULTS

The application of the eligibility criteria resulted in the inclusion of 35 primary studies published between 2015 and 2026. The sample consisted predominantly of randomized clinical trials of phases II and III, cardiovascular and renal outcomes studies, therapeutic withdrawal trials, and long-term extensions. Among the included studies, 17 evaluated GLP-1 receptor agonists, mainly liraglutide and semaglutide, 14 investigated

the dual GIP/GLP-1 agonist tirzepatide and four analyzed the triple GIP/GLP-1/glucagon agonist retatrutide.

The studied populations included adults with obesity or overweight, with or without type 2 diabetes mellitus, as well as

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patients with cardiovascular atherosclerotic disease,

heart failure with preserved ejection fraction, chronic kidney disease, liver disease associated with metabolic dysfunction, obstructive sleep apnea, and knee osteoarthritis. The follow-up period ranged from 24 weeks to approximately four years. The main findings by pharmacological strategy are summarized in Table 1.

Table 1. Summary of the Main Results by Pharmacological Strategy

Strategy Pharmacological	Studies included	Effect on weight and diabetes	Main outcomes systemic
GLP-1 receptor agonists: liraglutide and semaglutide	17	Liraglutide: approximate average weight loss of 6% to 8%. Semaglutide 2.4 mg: reduction close to 15% without diabetes and 9% to 10% with type 2 diabetes. Consistent improvement in glycosylated hemoglobin.	Reduction in cardiovascular events, renal progression, symptoms of heart failure, activity of liver disease, severity of sleep apnea, and osteoarthritis pain.
Dual GIP/ GLP-1 agonist: tirzepatide	14	Average loss of approximately 13% to 15% in people with diabetes and 20% or more in people without diabetes. Reductions in glycosylated hemoglobin are generally greater than two percentage points.	Benefits for heart failure, obstructive sleep apnea, metabolic liver disease, and preventing progression of prediabetes. Cardiovascular safety demonstrated versus dulaglutide.
Triple GIP/ GLP-1/glucagon agonist: retatrutide	4	Weight loss of up to 24.2% in a phase II study in obesity and up to 15.3% in a phase III trial in type 2 diabetes. Significant reduction in glycated hemoglobin.	Marked reduction in liver fat. No results from large studies of cardiovascular or renal outcomes had been published yet.

GLP-1 Receptor Agonists

Early studies with liraglutide demonstrated superior efficacy to placebo in reducing body weight in people with and

without type 2 diabetes. In the SCALE Obesity and Prediabetes study, liraglutide 3.0 mg produced an average reduction of approximately 8.0% in body weight, compared with 2.6% with placebo. The proportion of participants who achieved at least 5% weight loss was 63.2%, while 33. 1% reached

reduction greater than 10% (1). In patients with type 2 diabetes, the SCALE Diabetes study showed weight loss of approximately 6.0% with liraglutide 3.0 mg, 4.7% with the 1.8 mg dose, and 2.0% with placebo, accompanied by improved glycated hemoglobin and other metabolic parameters (2).

In individuals with obesity and obstructive sleep apnea, liraglutide reduced the apnea-hypopnea index to a greater extent than placebo, together with a 5.7% weight reduction, compared with 1.6% in the control group (3). In cardiovascular outcomes, the LEADER study demonstrated that liraglutide reduced the risk of the composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, with a hazard ratio of 0.87. Reductions in cardiovascular mortality and in all-cause mortality were also observed (4).

Semaglutide showed a greater magnitude of weight loss than liraglutide. In the STEP 1 study, adults with obesity or overweight without diabetes had an average weight reduction of 14.9% with semaglutide 2.4 mg, compared with 2.4% with placebo. Approximately half of the participants treated achieved at least 15% weight loss (6). In people with type 2 diabetes, STEP 2 demonstrated an average reduction of 9.6% with semaglutide 2.4 mg, 7.0% with semaglutide 1.0 mg, and 3.4% with placebo, along with a marked improvement in glycemic control (7).

The direct comparison from STEP 8 showed an average loss of 15.8% with semaglutide 2.4 mg and of 6.4% with liraglutide 3.0 mg, indicating a higher proportion of participants who achieved reductions of 10%, 15%, and 20% with semaglutide (10). In STEP 5, the mean weight loss of approximately 15.2% was maintained over 104 weeks, while the placebo group showed a reduction of 2.6% (11).

The withdrawal studies demonstrated dependence on continued therapy to maintain the results. In STEP 4, after an initial mean loss of

10.6% during the introduction phase, participants who remained on semaglutide lost more 7.9%, while those switched to placebo regained approximately 6.9% of body weight between weeks 20 and 68 (8) .

In cardiovascular studies, SUSTAIN-6 showed a reduction in major cardiovascular events with subcutaneous semaglutide in patients with type 2 diabetes and high cardiovascular risk. The primary endpoint occurred in 6.6% of treated participants and in 8.9% of the placebo group, corresponding to a hazard ratio of 0.74 (5) . In SELECT, conducted in people with obesity or overweight, established cardiovascular disease, and no diabetes, major cardiovascular events occurred in 6.5% of participants treated with semaglutide and in 8.0% of those who received placebo, with a hazard ratio of 0.80 (12) .

Oral semaglutide also reduced cardiovascular events in individuals with type 2 diabetes at high risk. In the SOUL study, the composite cardiovascular outcome occurred in 12.0% of treated patients and in 13.8% of participants in the placebo group, with a hazard ratio of 0.86 (17) .

In patients with type 2 diabetes and chronic kidney disease, the FLOW study showed a 24% reduction in the risk of the composite endpoint of renal progression, renal failure, or death from renal or cardiovascular causes. A smaller annual decline in the glomerular filtration rate, a reduction in cardiovascular events, and lower all-cause mortality were also observed (15).

In heart failure studies with preserved ejection fraction, semaglutide improved symptoms, functional capacity, and quality of life. In participants without diabetes, weight loss was 13.3% with semaglutide and 2.6% with placebo, along with improvements in the Kansas City Cardiomyopathy Questionnaire score and the six-minute walk test (13). In patients with type 2 diabetes, weight loss was 9.8% with semaglutide and 3.4% with placebo, also associated with clinical and functional improvement (14).

The systemic effects of semaglutide were also observed in the liver and the musculoskeletal system. In patients with steatohepatitis and fibrosis, resolution of steatohepatitis without worsening of fibrosis occurred in 59% of participants who received semaglutide 0.4 mg and in 17% of those who received placebo. However,

no statistically significant difference was observed in the outcome of improvement in fibrosis without worsening of steatohepatitis (9). In people with obesity and knee osteoarthritis, semaglutide resulted in 13.7% weight loss compared with 3.2% with placebo, along with a greater reduction in pain and improvement in physical function (16).

Dual GIP/GLP-1 Agonist

Tirzepatide promoted significant reductions in glycated hemoglobin and body weight at different stages of type 2 diabetes. In SURPASS-1, patients treated with diet and exercise showed reductions in glycated hemoglobin between 1.87 and 2.07 percentage points, depending on the dose, and lost up to 9.5 kg over 40 weeks (18) .

In SURPASS-2, tirzepatide was directly compared with semaglutide 1.0 mg in patients treated with metformin. Reductions in glycated hemoglobin ranged from 2.01 to 2.30 percentage points with tirzepatide and were 1.86 percentage point with semaglutide. Weight losses ranged from 7.6 to 11.2 kg with tirzepatide, compared with 5.7 kg with semaglutide (19) .

In patients with type 2 diabetes and high cardiovascular risk, SURPASS-4 demonstrated a greater glycemic reduction with tirzepatide than with insulin glargine. Body weight decreased by between 7.1 and 11.7 kg in the tirzepatide groups, while it increased by approximately 1.9 kg in the insulin-treated group (20) . In SURPASS-5, adding tirzepatide to insulin glargine reduced glycated hemoglobin by more than two percentage points and led to weight loss of up to 8.8 kg, while the placebo group experienced weight gain (21) .

In adults with obesity without diabetes, SURMOUNT-1 demonstrated mean losses of 15.0%, 19.5%, and 20.9% at doses of 5, 10, and 15 mg, respectively, compared with 3.1% with placebo. At doses of 10 and 15 mg, 50% and 57% of participants achieved weight loss of at least 20% of body weight (22) . In people with type 2 diabetes, SURMOUNT-2 showed reductions of 12.8% with 10 mg and 14.7% with 15 mg, compared with 3.2% with placebo (23) .

In SURMOUNT-3, participants who had lost at least 5% of body weight after an intensive lifestyle intervention were randomized to tirzepatide or placebo. Tirzepatide led to an additional reduction of approximately 18.4%, while the placebo group regained about 2.5% . Consi-

dering the entire study period, total weight loss was approximately 24.3% with tirzepatide (24) .

SURMOUNT-4 demonstrated the importance of therapeutic continuity. After an initial average reduction of 20.9%, participants who remained on treatment lost an additional 5.5%, while those transferred to placebo regained approximately 14.0%. At week 88, the cumulative loss was 25.3% in the continued treatment group and 9.9% in the withdrawal group (25).

In the direct comparison of SURMOUNT-5, tirzepatide promoted an average body weight reduction of 20.2%, while semaglutide 2.4 mg produced a reduction of 13.7%. At least 25% weight loss was achieved by 31.6% of participants treated with tirzepatide and by 16.1% of those who received semaglutide (30).

Regarding systemic outcomes, tirzepatide showed relevant results in obstructive sleep apnea. In the SURMOUNT-OSA trials, the reduction in the apnea-hypopnea index ranged from approximately 25 to 29 events per hour with tirzepatide, compared with reductions close to five events per hour with placebo. Reductions were also observed in hypoxic burden, body weight, systolic blood pressure, and Creative protein (26).

In metabolic dysfunction-associated steatohepatitis, resolution of the disease without worsening of fibrosis occurred in 44%, 56%, and 62% of participants treated with 5, 10, and 15 mg of tirzepatide, respectively, compared with 10% with placebo. Improvement of at least one stage of fibrosis without worsening of steatohepatitis occurred in approximately 51% to 55% of the tirzepatide groups and in 30% of the placebo group (27).

In the SUMMIT study, conducted in patients with obesity and heart failure with preserved ejection fraction, cardiovascular death or worsening of heart failure occurred in 9.9% of participants treated with tirzepatide and in 15.3% of those who received placebo, corresponding to a hazard ratio of 0.62. There was also improvement in symptoms and quality of life (28).

In the long-term follow-up of participants with obesity and prediabetes, type 2 diabetes was diagnosed during treatment in approximately 1.3% of patients who received tirzepatide and in 13.3% of those who received placebo. After the post-discontinuation observation period,

the proportions were approximately 2.4% and 13.7%, respectively (29).

In SURPASS-CVOT, tirzepatide was compared with dulaglutide in patients with type 2 diabetes and atherosclerotic cardiovascular disease. Major cardiovascular events occurred in 12.2% of participants treated with tirzepatide and in 13.1% of those who received dulaglutide. The hazard ratio was 0.92, demonstrating cardiovascular non-inferiority, with no statistically significant superiority (31) .

Triple Agonist GIP/GLP-1/glucagon

The four studies on retatrutide showed high weight and glycemic efficacy. In the phase II trial in adults with obesity or overweight without diabetes, the average weight reductions reached approximately 22.8% with 8 mg and 24.2% with 12 mg at 48 weeks, compared with 2.1% with placebo. The weight-loss trajectory had not yet reached a plateau by the end of follow-up (32) .

In patients with type 2 diabetes, the phase II study showed reductions in glycated hemoglobin of more than two percentage points at the highest doses, along with weight loss of up to approximately 16.9% over 36 weeks. Retatrutide achieved a greater weight reduction than dulaglutide 1.5 mg used as the active comparator (33) .

In the study of metabolic steatotic liver disease, the relative reduction in hepatic fat content ranged from approximately 42.9% to 82.4% at week 24, depending on the dose used. At the highest doses, normalization of hepatic fat content occurred in up to 86% of participants (34).

In the phase III trial TRANSCEND-T2D-1, conducted in people with type 2 diabetes inadequately controlled by diet and exercise, retatrutide reduced glycated hemoglobin glycated by by approximately 1.69, 1.86, and 1.94 percentage points at doses of 4, 9, and 12 mg, respectively, compared with 0.81 percentage point with placebo. Weight losses were 11.5%, 13.9%, and 15.3%, versus 2.6% in the placebo group. The composite endpoint of glycated hemoglobin equal to or below 6.5% and loss of at least 10% was achieved by 41% to 64% of treated participants, compared with 3% in the placebo group (35).

Safety and Tolerability

The most frequent adverse events among the three pharmacological strategies were gastrointestinal, especially nausea, diarrhea, vomiting, constipation, and abdominal discomfort. In general, these events were mild or moderate in intensity, occurred more frequently during dose escalation, and were more common in the intervention groups than in the control groups.

The studies with liraglutide and semaglutide reported a higher frequency of events related to the gallbladder compared with placebo. In SUSTAIN-6, complications of diabetic retinopathy were more frequent with semaglutide, mainly among participants with preexisting retinopathy and rapid reduction of glycated hemoglobin (5). In the tirzepatide studies, gastrointestinal events also accounted for the primary cause of discontinuation, occurring more frequently at higher doses.

In the retatrutide trials, nausea, diarrhea, and vomiting were the most reported events. A transient increase in heart rate was also observed, as well as infrequent dysesthesia and biliary events (32-35). No relevant episodes of severe hypoglycemia were identified when the medications were used without association with insulin or sulfonylureas.

Summary of Results

Studies demonstrated a progressive increase in the magnitude of weight loss from liraglutide to semaglutide, tirzepatide, and retatrutide. Liraglutide produced average reductions close to 6% to 8%, while semaglutide 2.4 mg reached approximately 15% in people without diabetes. Tirzepatide achieved average reductions of 20% or more in individuals without diabetes, and retatrutide showed weight loss of up to 24.2% in a phase II study.

In people with type 2 diabetes, the magnitude of weight reduction was generally lower than that observed in individuals without diabetes, although the glycemic improvements were significant. Tirzepatide and retatrutide produced reductions in glycated hemoglobin close to or greater than two percentage points at the highest doses.

Systemic benefits were more broadly documented with semaglutide and tirzepatide. Semaglutide showed evidence of reducing cardiovascular and kidney events, improving heart failure, osteoart-

hritis, and activity of metabolic liver disease. Tirzepatide showed favorable effects on heart failure, obstructive sleep apnea, steatohepatitis, and progression of prediabetes. Retatrutide demonstrated a marked reduction in liver fat, but it still did not have published results from large cardiovascular, kidney, or mortality outcome trials.

DISCUSSION

The findings of this integrative review demonstrate a substantial shift in the pharmacological treatment of obesity, marked by the transition from medications with moderate weight-impact effects to therapies capable of producing weight reductions close to those observed after some invasive metabolic interventions. The evolution of liraglutide to semaglutide, followed by the development of tirzepatide and retatrutide, shows that progressively broader modulation of incretin and metabolic pathways has enhanced both efficacy on body weight and the potential to control type 2 diabetes mellitus and its systemic complications.

Liraglutide represented a turning point by demonstrating that GLP-1 receptor agonism could be used specifically in the treatment of obesity. The SCALE studies showed average weight reductions of approximately 6% to 8%, accompanied by glycemic and cardiometabolic improvements in people with and without type 2 diabetes (1,2). Although this magnitude was lower than that observed with subsequent therapies, the results were clinically relevant, especially considering that weight losses greater than 5% may already be associated with improvements in metabolic risk factors. The benefit observed in obstructive sleep apnea also indicated early on that pharmacological reduction of adiposity could have an impact on organ complications related to excess weight (3).

The clinical relevance of liraglutide was broadened by the LEADER study, which demonstrated a reduction in major cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and high cardiovascular risk (4). This result contributed to changing the understanding of GLP-1 agonists, previously interpreted predominantly as hypoglycemic agents, into a class with the potent-

ial to modify cardiovascular prognosis. However, the weight loss observed in LEADER was relatively modest, suggesting that cardiovascular benefits do not depend exclusively on weight reduction. Improvements in inflammation, endothelial function, blood pressure, lipid profile, myocardial metabolism, and the stability of atherosclerotic plaque may have contributed to the clinical effect.

Semaglutide significantly increased the efficacy of isolated GLP-1 agonism. In the STEP studies, the 2.4 mg dose produced an average weight loss of nearly 15% in adults without diabetes, substantially outperforming the results obtained with liraglutide (6,10) . This superiority may be attributed to differences in pharmacological potency, half-life, weekly exposure, and the intensity of central action on hunger and satiety. The direct comparison of STEP 8 is particularly relevant, as it reduces limitations inherent to indirect comparisons between independent trials and confirmed greater weight-related efficacy of semaglutide compared with liraglutide 3.0 mg (10) .

Weight loss with semaglutide was lower in people with type 2 diabetes than in individuals without diabetes, as shown by the comparison between the STEP 1 and STEP 2 studies (6,7) . This pattern was also observed with tirzepatide and may be explained by different factors, including greater metabolic resistance, concomitant use of medications associated with weight gain, longer disease duration, impairment of beta-cell function, and reduced metabolic flexibility.

Even so, semaglutide provided a dual benefit in this population, combining weight reduction and improved glycated hemoglobin.

The duration of treatment proved decisive for maintaining the response. In STEP 4, replacing semaglutide with placebo was followed by a significant recovery of weight, whereas continued therapy promoted an additional reduction (8). STEP 5 showed that the effect can remain sustained for two years when the medication is maintained (11). These results reinforce the understanding of obesity as a chronic and relapsing disease, in which the physiological mechanisms that defend body weight remain active even after a substantial weight reduction. Stopping therapy favors the return of hunger, reduced satiety, and weight regain, simi-

lar to what can occur after discontinuation of treatments for other chronic diseases.

The SELECT study provided one of the most relevant pieces of evidence for recognizing obesity as an independent therapeutic factor. A 20% reduction in major cardiovascular events occurred in people who were overweight or obese and had established cardiovascular disease, but without diabetes (12). This finding showed that semaglutide's cardiovascular benefit is not limited to glycemic control. Weight loss, reduced systemic inflammation, improved blood pressure, lipid profile, and vascular function likely contributed in combination to the outcome.

Renal evidence was also strengthened by the FLOW study, in which semaglutide reduced the progression of chronic kidney disease and cardiovascular events in patients with type 2 diabetes (15). This benefit has high clinical relevance, considering the frequent association among obesity, diabetes, hypertension, albuminuria, and progressive loss of kidney function. However, interpretation should consider that the population presented disease renal predominantly albuminuric and that the use of sodium-glucose cotransporter type 2 inhibitors did not fully reflect current treatment patterns in all participants.

The STEP-HFpEF and STEPHFpEF DM studies demonstrated that semaglutide improved symptoms, functional capacity, and quality of life in patients with heart failure with preserved ejection fraction associated with obesity (13,14). In this condition, visceral adiposity, systemic inflammation, plasma volume expansion, ventricular stiffness, endothelial dysfunction, and physical limitation contribute to the pathophysiology. The clinical improvement observed suggests that treating obesity may act directly on central components of this heart failure phenotype. However, these studies were not designed to definitively demonstrate a reduction in cardiovascular mortality.

The results on the liver, sleep apnea, and osteoarthritis confirm that obesity should be analyzed as a multisystem disease. Semaglutide increased the resolution of steatohepatitis, although it did not initially show a statistically signific-

ant improvement in fibrosis (9). This difference may reflect the fact that reductions in steatosis and inflammation occur more quickly than remodeling of fibrotic tissue. In knee osteoarthritis, reduced pain and improved function accompanied substantial weight loss, possibly due to decreased mechanical load and inflammation related to adipose tissue (16).

Tirzepatide inaugurated a new phase by combining agonism of the GIP and GLP-1 receptors. The SURPASS studies showed marked reductions in glycated hemoglobin, often greater than two percentage points, associated with weight losses greater than those achieved with active comparators such as semaglutide 1.0 mg and insulin glargine (18-21). GLP-1 receptor agonism contributes to satiety, reduces glucagon, and promotes glucose-dependent insulin secretion, while activity at the GIP receptor may enhance the insulinotropic response and modify adipose tissue metabolism. The exact contribution of each receptor remains complex, since clinical efficacy depends on the pharmacodynamic balance between the two pathways.

In SURPASS-2, tirzepatide outperformed semaglutide 1.0 mg in glycemic control and weight loss (19). However, this comparison should not be interpreted as equivalence to a head-to-head with semaglutide 2.4 mg, a dose used specifically for obesity. This gap was later addressed by SURMOUNT-5, in which tirzepatide produced greater weight loss than semaglutide 2.4 mg (30). Even so, superiority in weight reduction does not automatically imply superiority in prevention
cardiovascular, renal, or mortality.

The SURMOUNT-1 trial demonstrated an average loss of up to 20.9% in individuals without diabetes, a result that brought drug therapy closer to magnitudes traditionally associated with metabolic surgery (22). However, surgery produces distinct anatomical, hormonal, and metabolic changes, and comparisons between these modalities must consider durability, risks, costs, access, nutritional effects, and the need for ongoing treatment. Drug therapy offers less invasiveness and greater potential for individualization, but its effectiveness depends on long-term adherence.

In people with type 2 diabetes, weight loss with tirzepatide was smaller than in individuals without diabetes, although it remained higher than that seen with several previous treatments (23). The combination of weight reduction, improved glycated hemoglobin, and a lower need for insulin intensification makes tirzepatide particularly relevant for patients in whom obesity and diabetes perpetuate each other.

The SURMOUNT-3 and SURMOUNT-4 studies provided important information on integration with behavioral interventions and on therapeutic maintenance (24,25). In SURMOUNT-3, tirzepatide increased the weight loss achieved after intensive lifestyle intervention, indicating that pharmacotherapy, appropriate diet, physical activity, and behavioral support should not be considered competing strategies. In SURMOUNT-4, discontinuation was accompanied by substantial weight regain, whereas continuation resulted in additional weight loss. As observed with semaglutide, this result supports the long-term treatment of obesity.

The systemic benefits of tirzepatide were particularly expressivos in obstructive sleep apnea. The reduction of approximately 25 to 29 respiratory events per hour in the SURMOUNT-OSA studies was greater than that observed previously with liraglutide (3.26). An important part of this benefit was probably mediated by loss of cervical, abdominal, and visceral fat. However, improvement in airway stability and respiratory function may also have occurred. Tirzepatide should not be interpreted as an automatic substitute for continuous positive airway pressure, especially in severe cases, but it may act as a complementary etiologic intervention.

In metabolic liver disease, tirzepatide increased both the resolution of steatohepatitis and the proportion of patients with improved fibrosis (27). This result was broader than the initial signal observed with semaglutide, although differences in population, duration, dose, and study design prevent a definitive direct comparison. Weight loss, improved insulin resistance, reduced lipotoxicity, and decreased hepatic inflammation may explain the results.

The SUMMIT study added important clinical evidence by demonstrating a reduction in cardiovascular death or worsening of heart failure in patients with

obesity and preserved ejection fraction (28) . The effect was driven mainly by a lower frequency of heart failure worsening, so it was not possible to claim an isolated reduction in mortality. Even so, the study strengthens the hypothesis that obesity is a central therapeutic target in this phenotype.

The reduction in the progression from prediabetes to type 2 diabetes during prolonged treatment with tirzepatide was significant (29). This benefit likely resulted from the combination of weight loss, improved insulin sensitivity, reduced demand on beta cells, and incretin modulation. The increase in cases after discontinuation, although still lower than that observed with placebo, shows that part of prevention depends on maintaining treatment and the weight lost.

In the cardiovascular setting, SURPASS-CVOT showed noninferiority of tirzepatide compared with dulaglutide, but not statistical superiority (31). This result should be interpreted precisely. The lack of superiority over a comparator with recognized cardiovascular benefit does not equate to the absence of cardioprotection. The study confirmed safety and presented a numerically favorable estimate, but it did not provide sufficient evidence to claim a greater reduction in events compared with dulaglutide.

Retatrutide represents the most recent stage of the therapeutic evolution analyzed. Its simultaneous action on GIP, GLP-1, and glucagon seeks to combine reduced food intake, improved glycemic control, and a potential increase in energy expenditure. Agonism of the glucagon receptor may favor fat mobilization and energy expenditure, but it also requires pharmacological balance to avoid hyperglycemia, excessive loss of lean body mass, or cardiovascular effects.

In the phase II study in obesity, retatrutide produced weight loss of up to 24.2%, with no evident plateau at week 48 (32). These results suggest potentially greater efficacy than earlier therapies, but they should be interpreted with caution due to the sample size, the absence of an active comparator, and the shorter follow-up duration. The results in type 2 diabetes confirmed marked glycemic and weight reduction (33,35), while the liver substudy showed a pronounced reduction in liver fat (34).

Despite the performance of retatrutide, the maturity of the evidence is still lower than what is available for semaglutide and tirzepatide. The included studies did not present results from large cardiovascular, renal, or mortality trials. In addition, the transient increase in heart rate, the occurrence of gastrointestinal events, and reports of sensory changes should be monitored in larger samples over longer periods. The magnitude of weight loss also requires assessment of body composition, as very marked reductions may involve loss of lean mass in addition to reduced adipose tissue.

Safety was a common aspect across the three strategies. Nausea, vomiting, diarrhea, constipation, and abdominal discomfort were the most frequent adverse events. In general, they occurred during dose escalation and were of mild or moderate intensity. However, they may compromise adherence and lead to treatment interruption. Gradual titration strategies, nutritional guidance, and clinical monitoring are relevant to improve tolerability.

Events related to the gallbladder were more frequent in some studies. This risk may result from both the pharmacological action and rapid weight loss. The occurrence of complications of retinopathy in SUSTAIN-6 also deserves attention, especially in patients with preexisting retinopathy and rapid reductions in glycated hemoglobin (5). This finding does not indicate directly proven ocular toxicity, but it reinforces the need for carefully planned ophthalmologic assessment and glycemic control in vulnerable individuals.

Another relevant aspect is hypoglycemia. GLP-l agonists, tirzepatide, and retatrutide have a low intrinsic risk of hypoglycemia because they stimulate insulin secretion in a glucose-dependent manner. However, the risk increases when they are used in combination with insulin or sulfonylureas, making it necessary to review the doses of these medications during the introduction of incretin-based therapy.

Preserving lean muscle mass should also be considered. Weight loss involves loss of adipose tissue and, to a lesser extent, lean mass. In elderly, frail, or sarcopenic patients, rapid and intense reduction can compromise strength, functionality, and independence. Thus, pharmacotherapy should be accompanied by

adequate protein intake, resistance training, and assessment of body composition when clinically indicated.

Comparisons between different classes must be carried out with caution. The trials varied in duration, presence of diabetes, initial weight, comorbidities, dose, statistical estimate, intensity of intervention
behavioral and management of missing data. Comparing percentages of weight loss across independent studies can lead to imprecise conclusions. Direct randomized comparisons have greater validity, such as STEP 8, SURPASS-2 and SURMOUNT-5
(10, 19,30).

The greatest weight efficacy observed with dual and triple agonists does not reduce the importance of GLP- 1–isolated agonists. Semaglutide has more mature evidence for cardiovascular and renal protection, while tirzepatide shows greater average efficacy on weight and glycemia and growing evidence in heart failure, sleep apnea, and liver disease. Retatrutide has the greatest weight potential observed in the database, but still lacks prolonged confirmation of safety and benefit on major clinical outcomes.

The selection of therapy should consider
the patient's individual profile, including the severity of obesity, the presence of diabetes, cardiovascular disease, kidney disease, heart failure, liver disease, sleep apnea, risk of sarcopenia, tolerability, preferences, access, and feasibility of long-term maintenance. There is no single strategy suitable for all patients. Greater weight loss is not the only therapeutic criterion, especially when the clinical priority is cardiovascular or renal protection.

This review highlights as strengths the inclusion of 35 primary studies, the predominance of randomized trials, the presence of active comparisons, and the assessment of outcomes beyond body weight. Incorporating cardiovascular,
renal, hepatic, respiratory, functional, and osteoarticular studies made it possible to analyze obesity as a systemic disease.

Among the limitations, the heterogeneity of the studies stands out, which prevented direct quantitative comparison. Most trials were funded by the manufacturers of the drugs, a frequent circumstance in pharmaceutical development, but one that requires attention to transparency, selective reporting, and the publicat-

ion of negative results. Some populations were underrepresented, and several studies had an insufficient duration to assess rare safety events, mortality, and maintenance over periods longer than five years.

Another limitation involves the scarcity of data on use in clinical practice, where adherence, access, cost-related interruptions, unavailability, incomplete titration, and a higher burden of comorbidities may reduce the effectiveness observed in trials.

There are also gaps regarding strategies after discontinuation, transition between medications, combinations with metabolic surgery, effects on bone and muscle mass, safety in frail populations, and implications of prolonged use.

Taken together, the findings indicate that incretin-based pharmacotherapy profoundly changed the treatment of obesity. The progression from isolated GLP-l agonism to dual GIP/GLP-l agonism and triple GIP/GLP-l/glucagon agonism expanded the magnitude of weight loss and metabolic benefits. However, the clinical value of these therapies should be determined not only by the percentage of weight reduction, but also by the ability to prevent cardiovascular and renal events, improve

systemic complications, preserve

functionality,present acc ceptable safety and maintain long-term results.

CONCLUSION

The findings of this integrative review demonstrated that pharmacotherapy for obesity undergoes a substantial change, driven by the evolution of isolated GLP-l receptor agonists toward dual GIP/GLP-l agonism and triple GIP/GLP-l/glucagon agonism strategies. This progression significantly expanded the magnitude of weight loss and glycemic control, while also showing clinical repercussions across cardiovascular, renal, hepatic, respiratory, musculoskeletal, and functional systems.

Liraglutide established the feasibility of GLP-l receptor agonism as a specific treatment for obesity, producing clinically relevant weight reduction and metabolic benefits. Semaglutide expanded this efficacy, achieving mean losses close to l5% in people without diabetes and providing strong evidence of reduced

cardiovascular events, renal protection, improved heart failure with preserved ejection fraction, reduced activity of metabolic fatty liver disease, and improved pain and function in patients with obesity-associated osteoarthritis.

Tirzepatide showed greater average efficacy on body weight and glycated hemoglobin, with losses exceeding 20% in individuals without diabetes and strong results in people with type 2 diabetes. Its effects extended to obstructive sleep apnea, steatohepatitis with fibrosis, heart failure associated with obesity, and a reduction in the progression of prediabetes to type 2 diabetes. Although it has demonstrated safety
cardiovascular versus dulaglutide, superiority over this comparator was not confirmed. for events major cardiovascular.

Retatrutide showed the highest percentages of weight loss among the studies analyzed, along with a marked reduction in glycated hemoglobin and liver fat content. However, the evidence available remains less mature than that for semaglutide and tirzepatide. The lack of consolidated results from large cardiovascular, renal, and mortality trials prevents its high weight-loss efficacy, at present, from being interpreted as a definitive overall systemic clinical benefit.

Withdrawal studies demonstrated that discontinuation of semaglutide or tirzepatide was accompanied by a significant recovery of body weight. This result confirms that obesity has a chronic and relapsing nature and that pharmacological treatment should be planned as a long-term strategy, combined with nutritional interventions, physical activity, and support behavioral and multidisciplinary follow-up. The therapeutic response should not be assessed exclusively by the percentage of weight lost, but also by improvement in comorbidities, functional capacity, quality of life, and the risk of major clinical events.

The events adverse gastrointestinal were the main limitation to tolerability among the therapies analyzed. Biliary events were also observed, as well as the need to pay attention to diabetic retinopathy in susceptible patients, the risk of hypoglycemia when the

medications were used together with insulin or sulfonylureas, and concern about preserving muscle mass during intensive weight losses. Thus, prescribing should be individualized and include gradual titration, periodic clinical assessment, nutritional guidance, and encouragement of resistance training.

The choice between isolated, dual, or triple agonists should consider the severity of obesity, the presence of type 2 diabetes, cardiovascular disease, chronic kidney disease, heart failure, liver disease, sleep apnea, frailty, risk of sarcopenia, tolerability, access, and the possibility of maintaining treatment. Greater weight-loss efficacy does not necessarily imply greater cardiovascular or renal protection; therefore, clinical decisions must integrate the quality and maturity of the available evidence for each outcome.

It is concluded that GLP-1 receptor agonists and the dual GIP/GLP-1 agonist have already significantly changed contemporary obesity treatment and its complications. Triple agonism is a promising perspective, but it still depends on confirmation of safety and efficacy in the long term. Future studies should clarify the durability of benefits, effects on mortality, body composition, bone and muscle health, and strategies after treatment interruption, transition between medications, application in underrepresented populations, and effectiveness in clinical practice. Consolidating this evidence may expand personalized obesity treatment and strengthen its recognition as a systemic disease that requires continuous, integrated, and risk-based care.

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