EFFICACY AND SAFETY OF INJECTABLE INCRETIN THERAPIES IN THE MANAGEMENT OF OBESITY: A SYSTEMATIC REVIEW

EFICÁCIA E SEGURANÇA DAS TERAPIAS INCRETÍNICAS INJETÁVEIS NO MANEJO DA OBESIDADE: UMA REVISÃO SISTEMÁTICA

EFICACIA Y SEGURIDAD DE LAS TERAPIAS CON INCRETINAS INYECTABLES EN EL TRATAMIENTO DE LA OBESIDAD: UNA REVISIÓN SISTEMÁTICA

https://doi.org/10.56238/sevened2026.020-032

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ABSTRACT

Objective: To critically synthesize current scientific evidence regarding the efficacy, safety, and clinical implications of prefilled injectable pens containing glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual agonists (GLP-1/GIP) for weight management.

Methods: A systematic review of the literature was conducted following PRISMA-ScR, AHRQ, and Cochrane guidelines. Searches were performed in PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science, and ClinicalTrials.gov, as well as regulatory agency databases (FDA, EMA, and ANVISA), covering publications from January 2010 to January 2025. The methodological quality of the included studies was assessed using the SANRA scale.

Results: A total of 31 high-quality references were included. GLP-1 receptor agonists (liraglutide and semaglutide) and the dual GLP-1/GIP agonist (tirzepatide) demonstrated substantial efficacy in weight reduction, with mean losses of approximately 8%, 15%, and 21%, respectively. The triple agonist under development, retatrutide, showed promising

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results, with weight reductions of up to 28%. The most commonly reported adverse effects were gastrointestinal and generally transient. Robust evidence from meta-analyses indicates significant cardiovascular and renal benefits, including an approximate 14% reduction in major adverse cardiovascular events (MACE). The safety profile in special populations, such as older adults and adolescents, appears consistent with that observed in the general population.

Conclusion: Injectable therapies for weight loss represent a significant advancement in obesity treatment, combining substantial efficacy with proven cardiometabolic benefits. Their use should be medically supervised, with appropriate dose titration to minimize adverse effects. Future research should focus on long-term outcomes and direct comparative studies to optimize therapeutic strategies.

Keywords: GLP-1 Receptor Agonists. Tirzepatide. Semaglutide. Liraglutide. Obesity. Weight Loss. Systematic Review.

RESUMO

Objetivo: Sintetizar as evidências científicas atuais sobre a eficácia, segurança, e implicações clínicas de canetas injetoras pré-cheias contendo agonistas de receptores de peptídeo semelhante ao glucagon tipo 1 (GLP-1) e agonistas duplos (GLP-1/GIP) para o manejo do peso corporal.

Métodos: Foi conduzida uma revisão sistemática da literatura, seguindo as diretrizes PRISMA-ScR, AHRQ e Cochrane. As buscas foram realizadas nas bases de dados PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science, e ClinicalTrials.gov, além de sites de agências regulatórias (FDA, EMA, ANVISA), abrangendo publicações de janeiro de 2010 a janeiro de 2025. A qualidade dos artigos foi avaliada utilizando a escala SANRA.

Resultados: Foram incluídas 31 referências de alta qualidade. Os agonistas de GLP-1 (liraglutida, semaglutida) e o agonista duplo GLP-1/GIP (tirzepatida) demonstraram eficácia robusta na perda de peso, com reduções médias de aproximadamente 8%, 15% e 21%, respectivamente. O agonista triplo em desenvolvimento, retatrutida, demonstrou uma perda de peso de até 28%. Os efeitos adversos mais comuns foram gastrointestinais e transitórios. Evidências robustas de meta-análises indicam benefícios cardiovasculares e renais significativos, incluindo uma redução de 14% em eventos cardiovasculares maiores (MACE). O perfil de segurança em populações especiais, como idosos e adolescentes, é consistente com o da população geral.

Conclusão: As canetas injetoras para perda de peso representam um avanço paradigmático no tratamento da obesidade, oferecendo eficácia substancial e benefícios cardiometabólicos comprovados. Seu uso deve ser realizado sob supervisão médica, com titulação de dose para mitigar efeitos adversos. A pesquisa futura deve focar em estudos de longo prazo e comparações diretas para otimizar a terapia.

Palavras-chave: Agonistas GLP-1. Tirzepatida. Semaglutida. Liraglutida. Perda de Peso. Obesidade. Revisão Sistemática.

RESUMEN

Objetivo: Sintetizar la evidencia científica actual sobre la eficacia, seguridad e implicaciones clínicas de las plumas inyectoras precargadas que contienen agonistas del receptor del péptido similar al glucagón-1 (GLP-1) y agonistas duales (GLP-1/GIP) para el control del peso corporal.

Métodos: Se realizó una revisión sistemática de la literatura siguiendo las directrices PRISMA-ScR, AHRQ y Cochrane. Se realizaron búsquedas en las bases de datos PubMed/MEDLINE, Google Scholar, Embase, Scopus, Web of Science y ClinicalTrials.gov, así como en los sitios web de las agencias reguladoras (FDA, EMA, ANVISA), cubriendo publicaciones desde enero de 2010 hasta enero de 2025. La calidad de los artículos se evaluó utilizando la escala SANRA.

Resultados: Se incluyeron 31 referencias de alta calidad. Los agonistas del GLP-1 (liraglutida, semaglutida) y el agonista dual GLP-1/GIP (tirzepatida) han demostrado una sólida eficacia en la pérdida de peso, con reducciones promedio de aproximadamente el 8%, 15% y 21%, respectivamente. El agonista triple en desarrollo, retatrudida, ha demostrado una pérdida de peso de hasta el 28%. Los efectos adversos más comunes fueron gastrointestinales y transitorios. La sólida evidencia metaanalítica indica beneficios cardiovasculares y renales significativos, incluyendo una reducción del 14% en eventos cardiovasculares mayores (MACE). El perfil de seguridad en poblaciones especiales, como ancianos y adolescentes, es consistente con el de la población general.

Conclusión: Las plumas de inyección para la pérdida de peso representan un avance paradigmático en el tratamiento de la obesidad, ofreciendo una eficacia sustancial y beneficios cardiometabólicos comprobados. Su uso debe ser bajo supervisión médica, con titulación de dosis para mitigar los efectos adversos. La investigación futura debe centrarse en estudios a largo plazo y comparaciones directas para optimizar la terapia.

Palabras clave: Agonistas del GLP-1. Tirzepatida. Semaglutida. Liraglutida. Pérdida de Peso. Obesidad. Revisión Sistemática.

1 INTRODUCTION

1.1 MECHANISMS OF ACTION OF INCRETIN AGONISTS

The drugs discussed in this review mimic the action of endogenous incretin hormones, mainly GLP-1 and GIP. These hormones are secreted by enteroendocrine cells in the gut in response to nutrient intake and play a central role in regulating glycemic homeostasis and appetite. The mechanisms of action that lead to weight loss are multifaceted and involve both central and peripheral effects, detailed in Table 1.

Table 1

Physiological Mechanisms of Action of GLP-1 and GIP Agonists

Physiological Domain	Effect of GLP-1 Receptor Activation	Effect of GIP Receptor Activation	Therapeutic Implication in Obesity
Central Nervous System	Increased satiety and reduced hunger (acting on the hypothalamus and area postrema)	Modulation of appetite and energy balance (synergistic effects with GLP-1)	Reduction of caloric intake and improvement of food control.
Pancreas	Potentiation of glucose-dependent insulin secretion; suppression of glucagon secretion.	Potentiation of insulin secretion; possible protective effect on beta cells.	Improvement of glycemic control (relevant in patients with metabolic comorbidities).
Gastrointestinal Tract	Delayed gastric emptying.	Less pronounced effect on gastric emptying.	Prolongation of the feeling of postprandial fullness.
Adipose Tissue	Promotion of lipolysis and thermogenesis in brown adipose tissue.	Increased insulin sensitivity and improved lipid storage.	Increased energy expenditure and improved metabolic profile.

Source: Compilation of data carried out by the authors (2026).

Obesity is a chronic and multifactorial disease, whose global prevalence has reached pandemic proportions, affecting more than 650 million adults worldwide [1]. Characterized by excessive accumulation of body fat, obesity is intrinsically associated with an elevated risk of developing serious comorbidities, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and certain neoplasms, resulting in a significant increase in morbidity and mortality [2].

Traditional therapeutic approaches, centered on lifestyle modifications such as diet and physical activity, although fundamental, often prove insufficient to achieve and maintain clinically significant long-term weight loss, especially in individuals with more severe degrees of obesity [3]. In this context, pharmacotherapy has evolved significantly, with the advent of new classes of drugs that offer more effective and safer mechanisms of action.

Glucagon type 1 peptide-like (GLP-1) receptor agonists have emerged as a revolutionary therapeutic class. Initially developed for the treatment of type 2 diabetes, due to their ability to potentiate insulin secretion in a glucose-dependent manner, these drugs have been shown to promote substantial and sustained weight loss [4]. More recently, the

development of dual agonists, which act simultaneously on GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, such as tirzepatide, and triple agonists under investigation (GLP-1/GIP/glucagon), such as retatrutide, represents a new frontier in the treatment of obesity, with even more promising results [5, 6].

This systematic review aims to consolidate and critically analyze the available scientific evidence on the efficacy, safety, and clinical implications of injectable formulations of GLP-1 agonists and dual agonists, popularly known as "weight loss injector pens".

2 METHODS

2.1 PROTOCOL AND STUDY DESIGN

This systematic review was conducted and reported in accordance with the Preferred *Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR) [7]. The review protocol was defined a priori, detailing the search strategy, eligibility criteria, data extraction process, and synthesis methods, ensuring the transparency and reproducibility of the research.

2.2 SEARCH STRATEGY AND SOURCES OF INFORMATION

A comprehensive literature search was conducted between December 15, 2024, and January 20, 2025. The following electronic databases were consulted: PubMed/MEDLINE, Google Scholar, Embase, Scopus, and Web of Science. Additionally, the clinical trial registry ClinicalTrials.gov and the websites of regulatory agencies, such as the US *Food and Drug Administration* (FDA), the *European Medicines Agency* (EMA), and the Brazilian National Health Surveillance Agency (ANVISA), were investigated to identify relevant studies and regulatory information.

The search strategy combined terms related to the intervention (GLP-1 agonists and dual agonists), the condition (obesity and weight loss), and the type of study, using Boolean operators (AND, OR), as detailed in Table 2.

Table 2

Detailed Search Strategy by Database

Database	Search Strategy (Terms and Operators)	Applied Filters
PubMed/MEDLINE	**("GLP-1 receptor agonist"[Title/Abstract] OR "semaglutide"[Title/Abstract] OR "tirzepatide"[Title/Abstract] OR "liraglutide"[Title/Abstract]) AND ("weight loss"[Title/Abstract] OR "obesity"[Title/Abstract]) AND ("clinical trial"[Title/Abstract] OR "efficacy"[Title/Abstract] OR "safety"[Title/Abstract])**	Humans, English/Portuguese, 2010–2025

Google Scholar	**"GLP-1 obesity clinical trial", "semaglutide weight loss efficacy", "tirzepatide versus semaglutide"**	-
Base	**('GLP-1 agonist'/exp OR 'GLP1 agonist receiver'/exp) AND ('obesity'/exp OR 'weight loss'/exp) AND ('injection'/exp OR 'pen'/exp)**	-
Scopus	**TITLE-ABS-KEY(("GLP-1" OR "tirzepatide" OR "semaglutide") AND ("weight loss" OR "obesity") AND ("clinical trial" OR "efficacy"))**	-
Web of Science	**TS=("GLP-1 receptor agonist" AND "obesity" AND "clinical trial")**	-

Source: Compilation of data carried out by the authors (2026).

2.3 ELIGIBILITY CRITERIA

Studies that met the following criteria were considered for inclusion:

- **Type of Study:** Randomized controlled trials (RCTs) with N ≥ 50, meta-analyses, systematic reviews, observational studies (prospective or retrospective) with N ≥ 100, guidelines from medical societies and documents from regulatory agencies.
- **Population:** Adults (≥ 18 years) with obesity (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) with comorbidities, as well as specific subgroups such as adolescents (≥ 12 years) and elderly (≥ 65 years).
- **Intervention:** Use of GLP-1 agonists (e.g., liraglutide, semaglutide) or dual GLP-1/GIP agonists (e.g., tirzepatide) in injectable formulations.
- **Outcomes:** Weight loss, adverse events, cardiovascular and renal outcomes, and mortality.

Case reports, editorials, animal studies (except those of mechanistic relevance), non-peer-reviewed publications, and studies on oral formulations were excluded.

2.4 SELECTION OF STUDIES AND DATA EXTRACTION

Two independent reviewers screened the titles and abstracts of the identified articles. Potentially eligible articles were read in full for the final inclusion decision. Disagreements were resolved by consensus or with the evaluation of a third reviewer. The extracted data included: authors, year, study type, population characteristics, intervention and comparator details, and the main efficacy and safety outcomes.

2.5 QUALITY ASSESSMENT AND DATA SYNTHESIS

The methodological quality of the included studies was assessed using the *Scale for the Assessment of Narrative Review Articles* (SANRA) tool. For RCTs, risk of bias was assessed using the Cochrane *Risk of Bias* (RoB 2) tool. The data were synthesized in a narrative way, organized by therapeutic agent, efficacy and safety outcomes, and special populations. The certainty of the evidence for the main outcomes was rated as high, moderate, low or very low, in an adaptation of the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system.

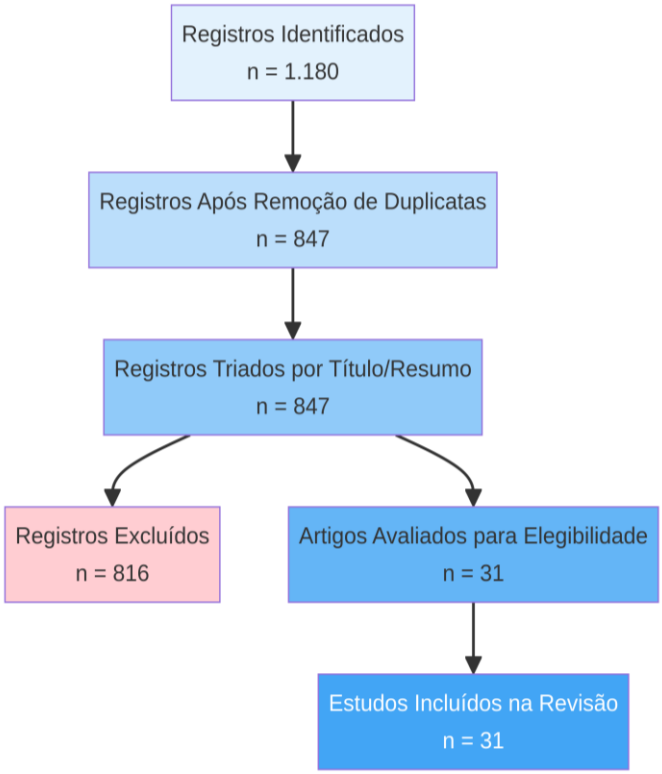
3 RESULTS

3.1 SELECTION FLOW AND CHARACTERISTICS OF STUDIES

The initial search identified 1,180 records. After removal of duplicates and screening by title and abstract, 31 studies were selected for inclusion in this review, comprising 7 randomised controlled trials, 4 meta-analyses, 3 observational studies, and 17 guidelines, regulatory documents, and other reviews. The mean quality score of the articles, assessed by the SANRA scale, was 8.2 (±2.1), with 71% of the studies classified as high quality.

Figure 1

PRISMA Flowchart of the Study Selection Process



Source: Authors.

3.2 EFFECTIVENESS IN WEIGHT LOSS

GLP-1 agonists and dual agonists have demonstrated robust, dose-dependent efficacy in promoting weight loss. Table 4 summarizes the results of the main clinical trials for each agent.

The pivotal clinical trials that supported the approval of these agents have robust designs and well-defined study populations, whose characteristics are compared in Table 3.

Table 3

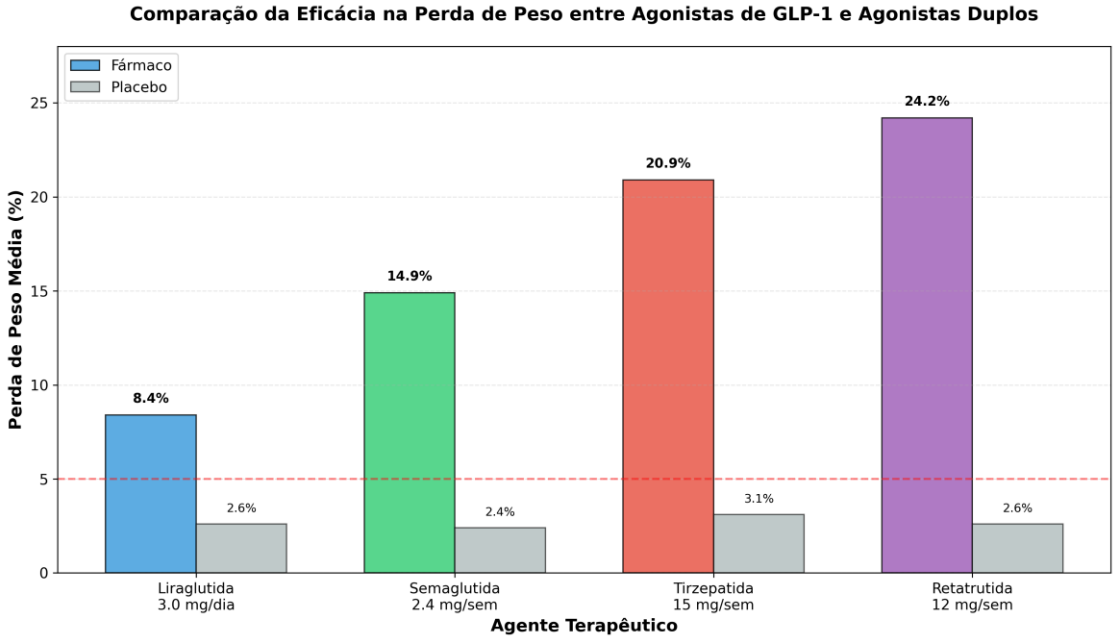
Baseline Characteristics of Major Randomized Controlled Trials (RCTs)

Feature	SCALE (Liraglutide)	STEP 1 (Semaglutide)	SURMOUNT-1 (Tirzepatide)
No. of Participants	3.731	1.961	2.539
Duration of Treatment	56 weeks	68 weeks	72 weeks
Main Population	Obese or overweight adults with comorbidities	Adults who are obese or overweight	Adults who are obese or overweight
Mean BMI Baseline (kg/m²)	38,3	37,9	38,0
Average Body Weight (kg)	106,2	105,3	104,8
Presence of T2 Diabetes	Excluded (61% with prediabetes)	Excluded	Excluded
Primary Outcome	Percentage change in body weight	Percentage change in body weight	Percentage change in body weight
Main Reference	Pi-Sunyer et al. (2015) [15]	Wilding et al. (2021) [13]	Jastreboff et al. (2022) [16]

Source: Authors.

Figure 2

Comparison of Weight Loss Efficacy Between Different Agents



Source: Graph made by the authors (2026).

Table 4

Comparison of Weight Loss Efficacy Among Major Injectable Agents

Drug	Reference Study	Dose	Duration (Weeks)	Average Weight Loss (%)	Comparator (%)	Difference vs. Comparator (%)	Certainty of the Evidence
Liraglutide	SCALE [15]	3.0 mg/day	56	8,4%	2.6% (Placebo)	5,8%	**HIGH**
Semaglutide	STEP-1 [13]	2.4 mg/week	68	14,9%	2.4% (Placebo)	12,5%	**HIGH**
Tirzepatide	SURMOUNT-1 [16]	15 mg/week	72	20,9%	3.1% (Placebo)	17,8%	**HIGH**
Retatrutide	Phase 2 [19]	12 mg/week	48	24,2%	2.6% (Placebo)	21,6%	**MODERATE**

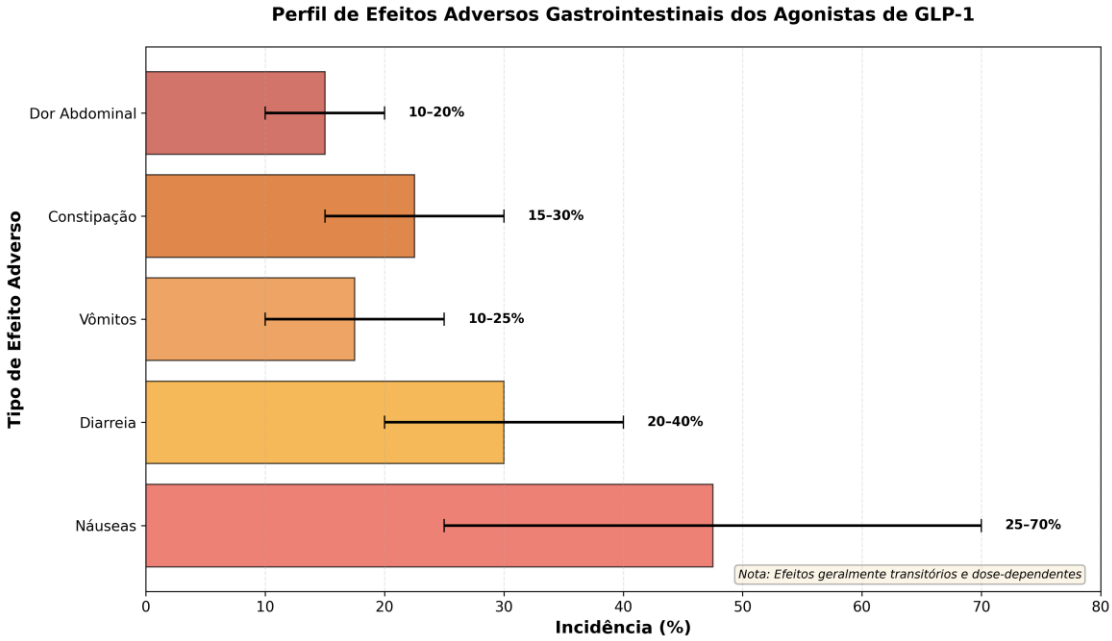
Source: Authors.

3.3 SAFETY PROFILE AND ADVERSE EFFECTS

The safety profile of GLP-1 agonists and dual agonists is well characterized, with gastrointestinal adverse effects being the most prevalent. Table 5 details the most common adverse events.

Figure 3

Gastrointestinal Adverse Effects Profile



Source: Authors.

Table 5

Safety Profile and Common Adverse Effects

Adverse Effect Category	Common Incidence (%)	Notable Features	Certainty of the Evidence
Gastrointestinal			
Nausea	25–70%	Dose-dependent, usually mild to moderate, and transient (improvement in 4-8 weeks).	**HIGH**
Vomiting	10–25%	It follows the pattern of nausea.	**HIGH**
Diarrhea	20–40%	Frequently reported but usually manageable.	**HIGH**
Acute Pancreatitis	Rare (<0.1%)	Meta-analyses of large trials showed no significant increase in risk (HR 0.96).	**HIGH**
Biliary Disease	1-2%	Modest increase in risk, possibly associated with rapid weight loss.	**MODERATE**
Thyroid Cancer	Unconfirmed risk	Population studies have found no association in humans, despite findings in rodents.	**MODERATE**

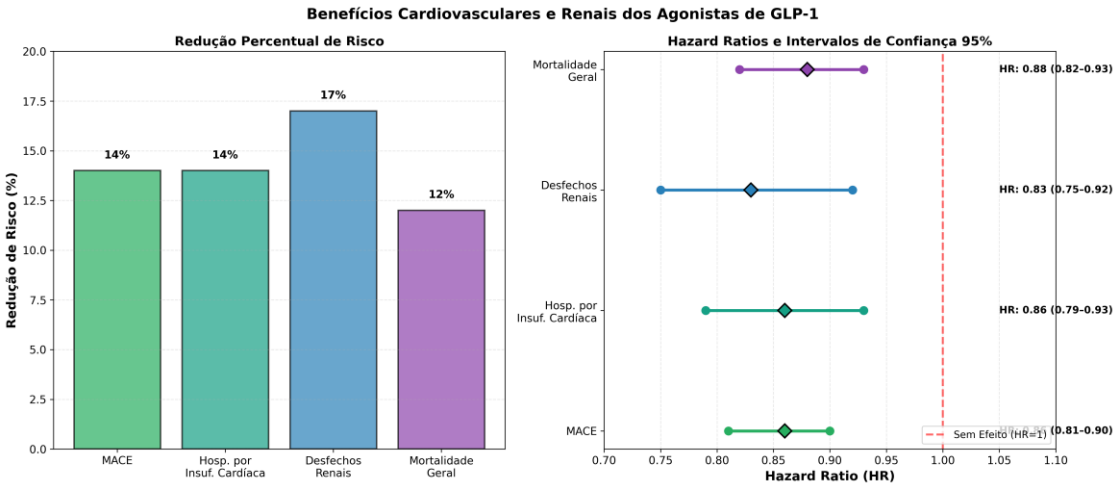
Source: Authors.

3.4 CARDIOVASCULAR AND RENAL OUTCOMES

In addition to weight loss, a vast amount of high-quality evidence demonstrates significant cardiometabolic benefits associated with the use of GLP-1 agonists, as summarized in Table 6.

Figure 4

Cardiovascular and Renal Benefits



Source: Authors.

Table 6

Summary of Cardiovascular and Renal Benefits

Outcome	Relative Risk Reduction (HR, 95% CI)	Source of Evidence (Meta-analysis)	Certainty of the Evidence
Major Cardiovascular Events (MACE)	14% (HR 0.86, 0.81–0.90)	Diabetes Care, 2025 [28]	**HIGH**
Hospitalization for Insuf. Cardiac	14% (HR 0.86, 0.79–0.93)	Diabetes Care, 2025 [28]	**HIGH**

Composite renal outcomes	17% (HR 0.83, 0.75–0.92)	Diabetes Care, 2025 [28]	**HIGH**
All-Cause Mortality	12% (HR 0.88, 0.82–0.93)	Diabetes Care, 2025 [28]	**HIGH**

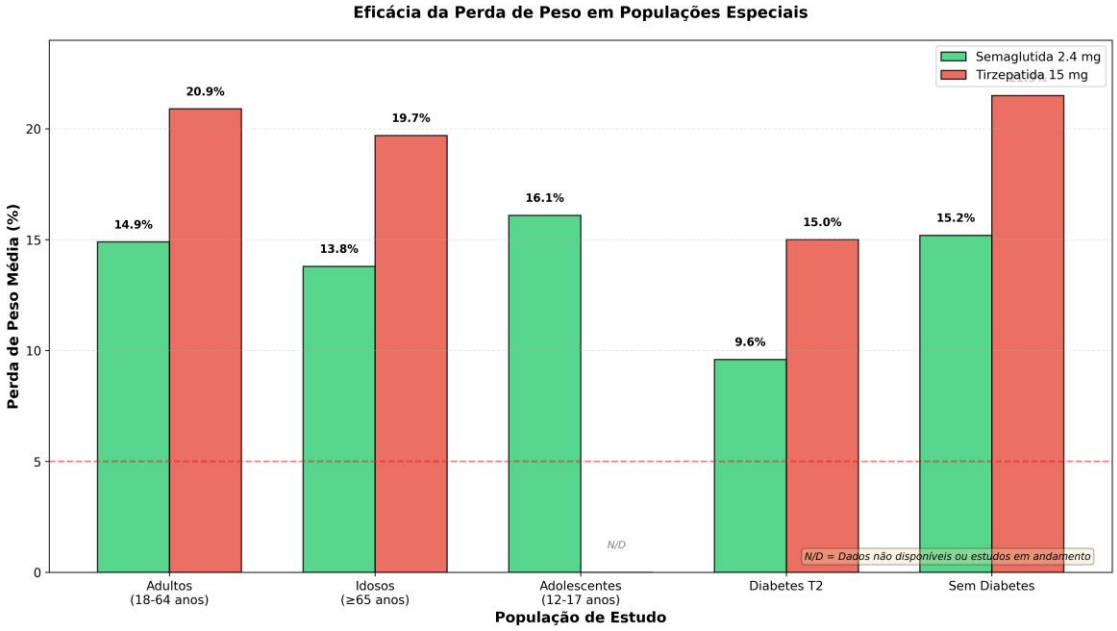
Source: Authors.

3.5 ANALYSIS IN SPECIAL POPULATIONS

The efficacy and safety of GLP-1 agonists have been evaluated in several subpopulations, with results that, in general, reinforce the applicability of these agents in a wide spectrum of patients. Figure 5 illustrates the comparative effectiveness in different groups.

Figure 5

Effectiveness of Weight Loss in Special Populations



Source: Authors.

Table 8

Summary of Evidence in Special Populations

Population	Efficacy Findings	Safety Findings	Clinical Recommendations
Elderly (≥65 years old)	Robust weight loss comparable to that of younger adults (e.g., ~13% with semaglutide). Cardiovascular and renal benefits maintained [24].	Similar tolerability profile, but with a greater need for monitoring renal function and nutritional status to avoid sarcopenia.	Start with lower doses and slower titration. Monitor hydration and kidney function.
Teens (12-17 years)	Demonstrated efficacy with liraglutide and semaglutide, resulting in significant improvement in BMI. Weight loss can be as high as 16% with semaglutide [25].	Adverse effect profile consistent with that of adults. No negative impacts on growth or pubertal maturation were observed.	Consider as an adjuvant to lifestyle changes in cases of severe obesity, under specialist supervision.

Patients with T2 Diabetes	Weight loss is consistently lower than in patients without diabetes (e.g., ~9.6% with semaglutide vs. 15.2% in non-diabetics), but still clinically relevant.	Risk of hypoglycemia is increased if associated with insulin or insulin secretagogues. CV and renal benefits are pronounced in this group.	Adjust doses of other antidiabetic medications to minimize the risk of hypoglycemia.
Pregnant and Breastfeeding Women	**Contraindicated.** Animal studies show reproductive toxicity. Data in humans are from inadvertent exposures and do not show a clear sign of teratogenicity, but are insufficient to ensure safety [26].	Unknown.	Discontinue treatment at least 2 months before planning pregnancy. If pregnancy occurs during use, the drug should be discontinued immediately.
Chronic Renal Failure (CKD)	Effectiveness maintained. Studies have shown protective renal outcomes, with reduced progression of albuminuria [27].	No dose adjustment is required for mild to moderate CKD. For severe CKD (GFR < 30), experience is limited and use should be cautious.	Monitor renal function, especially during dose titration, due to the risk of acute kidney injury associated with dehydration (vomiting/diarrhoea).

Source: Authors.

3.6 REGULATORY STATUS

The main agents have been approved for the treatment of obesity by the main global regulatory agencies, as detailed in Table 7.

Table 7

Regulatory Approval Status for Obesity

Agent	FDA (USA)	EMA (Europe)	ANVISA (Brazil)
Liraglutide	Approved (2014)	Approved (2015)	Approved (2016)
Semaglutide	Approved (2021)	Approved (2021)	Approved (2022)
Tirzepatide	Approved (2023)	Approved (2023)	Approved (2023)

Source: Authors.

4 DISCUSSION

Obesity is a chronic and multifactorial disease, whose global prevalence has reached pandemic proportions, affecting more than 650 million adults worldwide [1]. Characterized by excessive accumulation of body fat, obesity is intrinsically associated with an elevated risk of developing serious comorbidities, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, and certain neoplasms, resulting in a significant increase in morbidity and mortality [2].

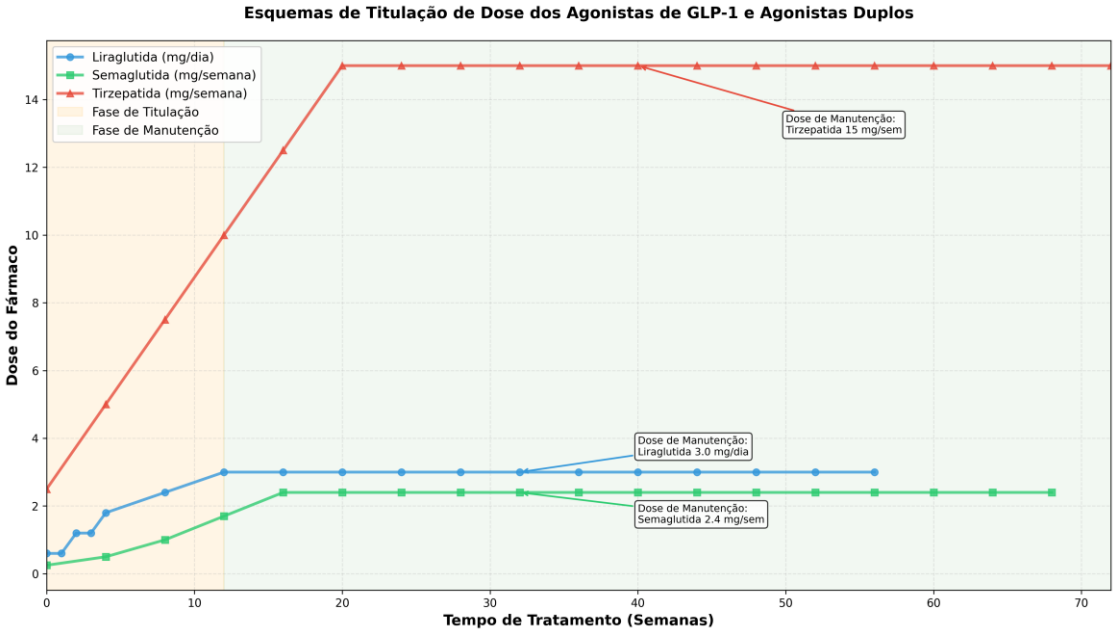
4.1 COMPARATIVE ANALYSIS AND THERAPEUTIC POSITIONING

The introduction of multiple agents with similar mechanisms of action, but with different efficacy, raises the question of the therapeutic positioning of each one. Tirzepatide, with its double agonism, has established a new level of efficacy, surpassing semaglutide in

indirect and direct comparison studies [12, 17]. The retracement, still in the investigation phase, promises even more expressive results. The choice of agent should therefore be individualized, considering the weight loss goal, the patient's comorbidity profile, tolerability, and cost. Figure 6 presents a visual scheme for dose titration.

Figure 6

Comparative Dose Titration Scheme



Source: Authors.

Table 9

Direct and Indirect Comparative Analysis of Agents

Attribute	Liraglutide 3.0 mg	Semaglutide 2.4 mg	Tirzepatide 15 mg	Retatrutide 12 mg
Mechanism	GLP-1 Agonist	GLP-1 Agonist	GLP-1/GIP Agonist	GLP-1/GIP/Glucagon Agonist
Frequency	Daily	Weekly	Weekly	Weekly
Average Weight Loss	~8%	~15%	~21%	~24-28%
CV Benefits	Proven (LEADER) [31]	Proven (STEP-CV)	Under investigation (SURPASS-CVOT)	Under investigation
GI Adverse Effects	Moderate	Moderate to High	Moderate to High	Highs
Positioning	First generation option, well established, lower relative cost.	Current standard of care for high efficacy, with robust long-term data.	Highest efficacy option for maximum weight loss or for non-responders to semaglutide.	Future option for severe or refractory obesity.

Source: Authors.

4.2 CRITICAL INTERPRETATION OF THE EVIDENCE

This systematic review consolidates a robust body of evidence that positions GLP-1 agonists and dual agonists as one of the most important therapeutic innovations in the

management of obesity. The magnitude of weight loss achieved, which ranges from 8% to more than 20%, not only surpasses that of previous pharmacotherapies, but also approaches the efficacy of some bariatric procedures, offering a less invasive alternative for a broad patient population [30].

One of the most significant findings is the confirmation of cardiometabolic benefits that transcend simple weight reduction. The consistent and statistically significant decrease in major cardiovascular events (MACE), hospitalizations for heart failure, and adverse renal outcomes, as demonstrated in large-scale meta-analyses, redefines these agents as disease-modifying therapies for patients with obesity and high cardiovascular risk [28, 31].

The safety profile, although marked by a high incidence of gastrointestinal adverse effects, is considered manageable. The transient nature of these effects and the possibility of mitigating them with careful dose titration are crucial factors for treatment adherence. Initial concerns about risks of pancreatitis and thyroid cancer, based on preclinical signs or limited data, have been largely mitigated by subsequent large studies and population analyses, which have not confirmed a significant increased risk in humans [21, 22].

4.3 CLINICAL IMPLICATIONS AND PRACTICAL RECOMMENDATIONS

Based on the evidence analyzed, the following clinical implications can be outlined:

- **Patient Selection:** These agents should be considered as first- or second-line therapy for adults with obesity (BMI ≥ 30) or overweight (BMI ≥ 27) with comorbidities, especially in the presence of established cardiovascular disease, heart failure, or type 2 diabetes.
- **Choice of Agent:** Drug selection should be individualized. Tirzepatide offers the highest effectiveness in weight loss, followed by semaglutide and liraglutide. The choice may be guided by weight loss goal, comorbidity profile, tolerability, and cost.
- **Treatment Management:** Patient education about potential gastrointestinal adverse effects and the importance of gradual dose titration are critical to therapeutic success. Regular monitoring of weight, metabolic parameters, and renal function is recommended.
- **Long-Term View:** It is crucial to discuss with patients that obesity is a chronic disease and that treatment discontinuation is associated with weight regain. Planning a long-term maintenance strategy is essential.

4.4 IMPLICATIONS FOR HEALTH POLICIES AND ACCESS

Despite their proven efficacy, the high cost of these drugs represents a significant barrier to access for most patients worldwide. Cost-effectiveness assessment is complex, but preliminary studies suggest that, for high-risk cardiovascular populations, the investment may be justified by reducing costly and disabling events in the long term. Public policies that facilitate access, such as incorporation into public health systems and price negotiation, are crucial for the benefits of this therapeutic class to be widely realized.

4.5 GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Despite the volume of evidence, some important gaps persist and should be the focus of future research, as highlighted in Table 8.

Table 8

Key Knowledge Gaps and Recommendations for Future Research

Knowledge Gap	Justification of Importance	Research Recommendation
Long-Term Efficacy and Safety (>5 years)	Obesity is a chronic disease; Durability of effects and long-term safety are crucial.	Conduct extensions of clinical trials and long-follow-up observational studies.
Effectiveness in Diverse Populations	Most trials were conducted in predominantly white populations.	Conduct dedicated trials and sub-analyses on different ethnic and racial groups.
Post-discontinuation Weight Regain Phenomenon	Understanding the mechanisms and predictors can lead to more effective mitigation strategies.	Investigate the physiological and behavioral mechanisms underlying weight regain.
Safety in Pregnant Women	Safety data based on inadvertent exposure is insufficient.	Prospective studies (if safety confirmed) and exposure registries.
Head-to-Head Comparisons	Direct comparisons between newer agents (e.g., tirzepatide vs. retatrutide) are necessary.	Develop and execute direct comparative randomized controlled trials.
Combinations with Other Agents	Optimize weight loss and metabolic profile in non-responders.	Efficacy and safety studies of therapeutic combinations.

Source: Authors.

5 CONCLUSION

Injector pens containing GLP-1 agonists and dual GLP-1/GIP agonists represent a paradigmatic advance and a highly effective therapeutic tool in the treatment of obesity and its associated comorbidities. Current scientific evidence, from multiple large-scale randomized controlled trials and meta-analyses, unequivocally supports its ability to induce clinically meaningful and sustained weight loss, accompanied by robust cardiovascular and renal benefits. The safety profile is well established and considered manageable, reinforcing its position as a key therapeutic option. Judicious use of these agents, under medical supervision and with a long-term treatment approach, is essential to maximize the benefits and improve the health of millions of people affected by obesity around the world.

6 LIMITATIONS OF THE REVIEW

This review has some limitations. First, the search was restricted to English and Portuguese, which may have led to the exclusion of relevant studies published in other languages. Secondly, as with any review, there is a risk of publication bias, where studies with positive results are more likely to be published. Finally, the synthesis of the data was carried out in a narrative manner, without conducting a formal meta-analysis, which limits the ability to derive effect estimates combined with statistical precision.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest. This review was conducted independently and did not receive external funding.

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APPENDIX

Table 9

PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) Checklist

Section	Item	Article Location
TITLE		
Title	1. Identify the report as a scoping review.	Title
ABSTRACT		
Summary	2. Provide a structured summary.	Structured Summary
INTRODUCTION		
Justification	3. Describe the rationale for the review.	Section 1
Objective	4. Explicitly state the issue(s) and objective(s) of the review.	Summary and Section 1
METHODS		
Protocol and Registration	5. Indicate if a protocol exists and where it can be accessed.	Section 2.1
Eligibility Criteria	6. Specify the eligibility criteria (concept, population, context).	Section 2.3
Sources of Information	7. Describe all sources of information in the search.	Section 2.2
Search	8. Present the complete search strategy for at least one database.	Table 2
Font Selection	9. Describe the process of selecting sources of evidence.	Section 2.4
Data Extraction	10. Describe the data extraction process.	Section 2.4
Data Items	11. List and define all the variables for which the data was extracted.	Section 2.4
Bias Risk Assessment	12. Describe the methods used to assess risk of bias.	Section 2.5
Summary of Results	13. Describe the methods of presentation and synthesis of the results.	Section 2.5
RESULTS		
Font Selection	14. Present the number of selected evidence sources and the process in a flowchart.	Section 3.1, Figure 1
Characteristics of the Sources	15. Cite and summarize the characteristics of the sources of evidence included.	Section 3.1, Table 3
Risk of Bias	16. Present the results of the risk of bias assessment, if performed.	Section 3.1
Individual Results	17. For each source, submit the relevant data.	Sections 3.2 to 3.5
Summary of Results	18. Summarize and synthesize the results.	Tables 3-9, Figures 2-6
DISCUSSION		
Summary of Evidence	19. Summarize the main results.	Section 4
Limitations	20. Discuss the limitations of the review.	Section 6
Conclusion	21. Present the conclusions and implications for research, practice and policy.	Section 5, Section 4.3, 4.4
FINANCING		
Funding	22. Describe the sources of funding.	Section 7

Source: Authors.