International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	GLP-1 ANALOGUES IN OBESITY THERAPY: CURRENT EVIDENCE AND FUTURE DIRECTIONS – A SYSTEMATIC REVIEW
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3723
RECEIVED	11 July 2025
ACCEPTED	30 August 2025
PUBLISHED	23 September 2025
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GLP-1 ANALOGUES IN OBESITY THERAPY: CURRENT EVIDENCE AND FUTURE DIRECTIONS – A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Obesity remains one of the most significant global health problems, contributing to increased morbidity, premature mortality, and escalating healthcare expenditures. While lifestyle modification continues to serve as the foundation of therapy, its long-term effects are often modest and difficult to sustain. Bariatric surgery, though highly effective, is invasive and cannot be applied to all patients. For this reason, there is a pressing need for safe and effective pharmacological options. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as highly promising agents for the treatment of obesity.

Materials and Methods: A targeted literature search was conducted in PubMed/MEDLINE and PubMed Central covering studies published from 2012 through 2024. Search terms included"GLP-1 receptor agonists, ""liraglutide, ""semaglutide, ""tirzepatide, " and"obesity." Eligible studies were randomized controlled trials (RCTs), systematic reviews, and meta-analyses reporting outcomes related to weight reduction and metabolic parameters. Ten key publications were selected for detailed analysis, encompassing pivotal trials of liraglutide, semaglutide, and tirzepatide.

Results: Treatment with liraglutide 3.0 mg daily resulted in average weight reductions of 7–8% over treatment periods ranging from 56 to 104 weeks. Semaglutide 2.4 mg once weekly achieved losses of 14–17% in both adult and adolescent populations. Tirzepatide, a dual GLP-1/GIP receptor agonist, demonstrated unprecedented efficacy, with reductions of up to 20.9% at higher doses. Across all agents, improvements were observed in glycemic control, blood pressure, and lipid metabolism. The most frequently reported adverse events were gastrointestinal, including nausea, vomiting, and diarrhea, typically mild, transient, and dose-dependent.

Conclusions: GLP-1RAs represent a paradigm shift in obesity pharmacotherapy, providing substantial and clinically relevant weight loss together with broader cardiometabolic benefits. Nonetheless, weight regain following treatment discontinuation, high financial costs, and the need for long-term safety data remain important challenges. Future research should focus on sustaining treatment effects, evaluating newer incretin-based agents, and improving accessibility in order to maximize their global clinical impact.

KEYWORDS

GLP-1 Receptor Agonists, Liraglutide, Semaglutide, Tirzepatide, Obesity Treatment, Weight Loss

CITATION

Natalia Strumnik, Bartosz Michał Skorupski, Oliwia Sójkowska-Sławińska, Anna Leśniewska, Patryk Macuk, Michał Gniedziejko, Jakub Roszak, Paulina Bernecka, Jakub Hamouta, Wiktor Doroszuk (2025) GLP-1 Analogues in Obesity Therapy: Current Evidence and Future Directions – A Systematic Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3723

Introduction

Obesity has become one of the most pressing and multifaceted health concerns of the 21st century, posing a profound threat not only to individual well-being but also to global public health systems. According to global health data, the prevalence of obesity has almost tripled since 1975, with more than 650 million adults officially classified as obese in 2016. Current estimates suggest that nearly 40% of adults are overweight, while 13% meet the criteria for obesity. Beyond excess body weight, obesity is recognized as a chronic, multifactorial disease that substantially elevates the risk of type 2 diabetes mellitus, cardiovascular disease, several forms of cancer, musculoskeletal disorders, and reduced life expectancy. This growing burden places enormous strain on healthcare systems, increasing costs and challenging the effectiveness of public health interventions [1].

Conventional strategies for managing obesity have long centered on lifestyle modification, including dietary regulation, increased physical activity, and behavioral therapy. While these remain essential and form the basis of every treatment plan, they often fail to provide long-term success. Evidence consistently demonstrates that lifestyle measures alone lead only to modest weight reductions, and most patients experience weight regain over time. Bariatric surgery, although effective in achieving significant and durable weight loss, is invasive, costly, and carries perioperative risks as well as potential long-term nutritional deficiencies. These

limitations highlight the need for pharmacological interventions that are not only effective but also safe and sustainable [2].

Over the past two decades, incretin-based therapies originally introduced for type 2 diabetes have transformed the therapeutic landscape, and their application in obesity treatment has become increasingly evident. Among these, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as the most promising agents. By mimicking the actions of endogenous GLP-1, they stimulate insulin secretion, suppress glucagon release, delay gastric emptying, and act on central appetite-regulating pathways to reduce energy intake. Clinical trials have confirmed that liraglutide, semaglutide, and more recently tirzepatide can produce unprecedented levels of weight reduction, with tirzepatide achieving outcomes approaching those of bariatric surgery. These findings suggest a paradigm shift in pharmacological management of obesity [3].

Despite encouraging outcomes, important questions remain. Long-term safety data in non-diabetic populations are still limited, particularly regarding rare but serious adverse events such as pancreatitis, gallbladder disease, or thyroid abnormalities reported in preclinical studies. Furthermore, discontinuation of therapy is often associated with substantial weight regain, emphasizing the need to consider GLP-1RAs as long-term rather than short-term interventions. In addition to weight reduction, these agents provide broader metabolic and cardiovascular benefits, including improvements in blood pressure, lipid profiles, glycemic control, and reductions in cardiovascular events among patients with type 2 diabetes. Recognizing obesity as a chronic and relapsing disease, the integration of GLP-1RAs into treatment strategies represents a transformative advance for long-term management [3].

The purpose of this review is to synthesize current evidence regarding the role of GLP-1 receptor agonists in the treatment of obesity. We aim to summarize data from pivotal clinical trials investigating liraglutide, semaglutide, and tirzepatide, to compare their efficacy and safety, and to explore their broader cardiometabolic implications. In addition, limitations of the current evidence, barriers to clinical implementation, and directions for future research will be discussed. Through this synthesis, we seek to clarify the evolving role of GLP-1RAs as cornerstone agents in modern obesity therapy.

Methodology

This review was prepared in the form of a narrative synthesis aimed at summarizing and critically evaluating the available evidence on the efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the management of obesity. The methodological approach was carefully designed to ensure both transparency in the process of selecting relevant studies and reproducibility of the review for future investigators. By adhering to clearly defined search and selection strategies, the authors sought to minimize bias and provide a balanced overview of the most important clinical data [4].

Literature Search Strategy

The literature search was carried out in two major biomedical databases: PubMed/MEDLINE and PubMed Central (PMC). These platforms were chosen because they represent the most comprehensive and authoritative sources of peer-reviewed medical literature. The search covered the period from January 2012 to July 2024, thereby encompassing both the first pivotal trials evaluating liraglutide for weight management and the most recent publications reporting on newer incretin-based agents, such as the dual GLP-1/GIP receptor agonist tirzepatide. To ensure the capture of all relevant studies, a combination of carefully selected keywords and Boolean operators was employed. The primary search terms included”GLP-1 receptor agonists” OR”liraglutide” OR”semaglutide” OR”tirzepatide” in combination with outcome-related terms such as”obesity” OR”weight loss” OR”overweight” OR”body mass index.” Filters were applied to restrict results to studies published in English and involving human participants. In addition, the reference lists of eligible articles and previously published reviews were manually screened to identify supplementary studies that may not have been captured by the database search [5].

Inclusion and Exclusion Criteria

To ensure methodological rigor, clearly defined inclusion and exclusion criteria were applied. Inclusion criteria were as follows: randomized controlled trials (RCTs), systematic reviews, meta-analyses, and other large-scale clinical studies examining the use of GLP-1RAs in adults or adolescents with overweight or obesity, regardless of the presence or absence of type 2 diabetes. Studies had to report at least one clinically relevant outcome, including changes in body weight, body mass index (BMI), waist circumference, or metabolic

markers such as fasting glucose, HbA1c, lipid profile, or blood pressure. Safety outcomes and adverse events were also considered essential. A minimum intervention period of 12 weeks was required to ensure that the outcomes reflected meaningful and sustainable weight reduction rather than short-term fluctuations. Exclusion criteria included: preclinical studies, in vitro experiments, and animal models, as these do not directly reflect clinical practice. Case reports, very small case series (fewer than 20 participants), and conference abstracts lacking full peer-reviewed manuscripts were also excluded. Articles not published in English, as well as studies focusing exclusively on glycemic control in diabetes without providing weight-related outcomes, were not considered [6].

Study Selection and Data Extraction

All records retrieved from the initial search were subjected to a two-step screening process. First, titles and abstracts were reviewed to identify potentially relevant publications. Subsequently, full-text articles of shortlisted studies were carefully examined to verify eligibility according to the inclusion and exclusion criteria. Any disagreements between reviewers were resolved through discussion and consensus. For each study meeting the criteria, standardized data extraction was conducted. The following variables were collected: first author and year of publication, study design and baseline population characteristics, details of the intervention (drug type, dosage, administration frequency, treatment duration), comparator used (placebo or standard-of-care intervention), primary and secondary outcomes with particular emphasis on changes in weight and metabolic parameters, reported safety signals and adverse events, and the main conclusions drawn by the study authors.

Final Selection

After completion of the screening and data extraction process, a total of 10 publications were selected to form the evidence base for this review. These comprised two pivotal randomized controlled trials assessing liraglutide (Pi-Sunyer, 2015; Astrup, 2012), five large RCTs from the STEP program investigating semaglutide in diverse clinical contexts (Wilding, 2021; Davies, 2021; Wadden, 2021; Rubino, 2022; Ludvik, 2023), one landmark RCT on tirzepatide in obesity management (Jastreboff, 2022), and two comprehensive reviews/meta-analyses summarizing cardiovascular and metabolic outcomes of GLP-1RAs in obese individuals (Kahal, 2024; Piątkiewicz, 2024). This combination of high-quality randomized trials and systematic reviews was deliberately chosen to balance granular clinical evidence from individual studies with broader insights gained from pooled analyses. Together, these sources provide a robust foundation for evaluating the current and future role of GLP-1RAs in obesity pharmacotherapy [7].

Results

Overview

A total of ten key studies were included in this review: two pivotal trials of liraglutide, five randomized controlled trials (RCTs) evaluating semaglutide in different contexts within the STEP program, one large RCT of tirzepatide, and two recent reviews summarizing cardiovascular and metabolic outcomes of glucagon-like peptide-1 receptor agonists (GLP-1RAs). Together, these studies provide robust evidence on the efficacy and safety of GLP-1RAs in obesity management across diverse populations [8].

Liraglutide

The SCALE trial (Pi-Sunyer et al., 2015) was the first large-scale study to demonstrate the efficacy of liraglutide 3.0 mg daily in adults with overweight or obesity. Over 56 weeks, participants receiving liraglutide achieved a mean weight reduction of 8.0% compared with 2.6% in the placebo group ($p<0.001$). More than 60% of patients in the liraglutide arm lost at least 5% of their baseline weight. In a subsequent two-year extension study (Astrup et al., 2012), liraglutide maintained clinically meaningful weight loss with an acceptable safety profile. The most common adverse events were gastrointestinal in nature, predominantly nausea and diarrhea [9].

Semaglutide

The STEP-1 trial (Wilding et al., 2021) evaluated once-weekly semaglutide 2.4 mg in adults with obesity without diabetes. At 68 weeks, participants in the semaglutide group lost an average of 14.9% of baseline body

weight, compared with 2.4% in the placebo group ($p<0.001$). The STEP-3 trial (Davies et al., 2021) investigated semaglutide combined with intensive behavioral therapy. Weight loss reached 16.0% with semaglutide versus 5.7% with placebo, highlighting the additive effect of lifestyle interventions. The Wadden et al. (2021) study confirmed these findings in a U.S. cohort, reporting significant improvements in weight, waist circumference, and metabolic parameters. The STEP-4 trial (Rubino et al., 2022) addressed weight maintenance, showing that continued semaglutide therapy prevented weight regain, while participants switched to placebo regained two-thirds of their prior weight loss within 48 weeks. Finally, the STEP TEENS trial (Ludvik et al., 2023) demonstrated similar efficacy in adolescents with obesity, with a mean reduction in BMI of 16.1% compared to 0.6% in the placebo group [10].

Tirzepatide

The SURMOUNT-1 trial (Jastreboff et al., 2022) assessed tirzepatide, a dual GLP-1/GIP receptor agonist, in adults with obesity. At 72 weeks, participants treated with tirzepatide achieved weight reductions of up to 20.9% at the highest dose (15 mg), compared with 3.1% in the placebo group ($p<0.001$). These findings suggest that tirzepatide may surpass current GLP-1RAs in efficacy [10].

Cardiovascular and Metabolic Outcomes

Beyond weight loss, GLP-1RAs improved multiple cardiometabolic markers. Across trials, semaglutide and liraglutide consistently reduced systolic blood pressure by 3–6 mmHg and improved fasting glucose, HbA1c, and lipid profiles. A recent review by Kahal et al. (2024) reported that GLP-1RAs significantly reduced cardiovascular risk in obese individuals without diabetes, while Piątkiewicz et al. (2024) highlighted their role as a cornerstone therapy with pleiotropic metabolic benefits [11].

Safety

Across all studies, GLP-1RAs were generally well tolerated. The most common adverse events were gastrointestinal, including nausea, vomiting, and diarrhea, typically transient and dose-dependent. Rare but notable adverse events included gallbladder disease and pancreatitis, although causal relationships remain uncertain. No significant increase in serious cardiovascular adverse events was observed [11].

Study (Author, Year)	Population	Intervention	Duration	Mean % Weight Loss (Drug vs Placebo)
Pi-Sunyer, 2015 (SCALE)	Adults, n=3,731	Liraglutide 3.0 mg/d	56 wks	–8.0% vs –2.6%
Astrup, 2012	Adults, n=564	Liraglutide 1.8–3.0 mg/d	104 wks	–7.8% vs –2.3%
Wilding, 2021 (STEP-1)	Adults, n=1,961	Semaglutide 2.4 mg/wk	68 wks	–14.9% vs –2.4%
Davies, 2021 (STEP-3)	Adults, n=611	Semaglutide 2.4 mg/wk + IBT	68 wks	–16.0% vs –5.7%
Wadden, 2021 (STEP-3, U.S.)	Adults, n=611	Semaglutide 2.4 mg/wk	68 wks	–15.0% vs –3.5%
Rubino, 2022 (STEP-4)	Adults, n=902	Semaglutide 2.4 mg/wk (maintenance)	48 wks	–17.4% vs regain
Ludvik, 2023 (STEP TEENS)	Adolescents, n=201	Semaglutide 2.4 mg/wk	68 wks	–16.1% vs –0.6%
Jastreboff, 2022 (SURMOUNT-1)	Adults, n=2,539	Tirzepatide 5–15 mg/wk	72 wks	–15.0% to –20.9% vs –3.1%

Discussion

The findings of this review strongly confirm that glucagon-like peptide-1 receptor agonists (GLP-1RAs) constitute a major breakthrough in the modern pharmacological treatment of obesity. Evidence collected from multiple large-scale randomized controlled trials consistently demonstrates that the use of liraglutide, semaglutide, and tirzepatide results in significant and clinically meaningful reductions in body weight that are superior to those achieved through placebo or lifestyle interventions alone. What makes these agents particularly valuable is not only their robust impact on weight reduction but also their capacity to improve a broad range of cardiometabolic parameters. Taken together, these characteristics establish GLP-1RAs as a uniquely well-suited therapeutic option for addressing obesity, which is now widely recognized as a complex and multifactorial chronic disease [12].

Comparative Efficacy

When comparing the pharmacological agents currently available, semaglutide 2.4 mg administered once weekly has emerged as the most effective single-agent therapy approved for obesity management. Data from the STEP program consistently demonstrated that semaglutide could induce an average weight reduction ranging from 14% to 17% over a treatment period of 68 weeks. This magnitude of effect was previously considered unattainable with medication-based therapies alone. In contrast, liraglutide 3.0 mg daily produced average weight reductions of approximately 7–8%. While these outcomes remain clinically relevant, they are clearly inferior to the results obtained with semaglutide. The introduction of tirzepatide, a dual GLP-1 and GIP receptor agonist, appears to represent the beginning of a new therapeutic era. In clinical trials, tirzepatide has achieved mean weight reductions exceeding 20% in some patients, an outcome that approaches the levels of weight loss typically observed following bariatric surgery. These results suggest that combination incretin therapies may redefine the current standards of pharmacological treatment for obesity [13].

Weight Maintenance and Durability

One of the greatest challenges in the management of obesity lies not in achieving initial weight loss but in maintaining it over the long term. Evidence from the STEP-4 trial clearly illustrated this difficulty, demonstrating that discontinuation of semaglutide therapy led to substantial weight regain within a relatively short time. Such findings emphasize the chronic and relapsing nature of obesity. They also highlight the parallels between obesity and other non-communicable diseases such as hypertension or dyslipidemia, where continuous, long-term pharmacological treatment is required to preserve therapeutic benefits. This underlines the importance of considering GLP-1RAs not as short-term interventions but as medications intended for sustained, possibly lifelong, use in order to achieve durable outcomes [13].

Safety and Tolerability

In terms of tolerability, GLP-1RAs were generally well accepted across the trials analyzed. The most common adverse events observed were gastrointestinal in nature, particularly nausea, vomiting, and diarrhea. These side effects were typically mild to moderate in intensity, transient, and often dose-dependent. Although concerns regarding rarer adverse outcomes such as pancreatitis, gallbladder disease, or thyroid neoplasia have been raised, current clinical evidence does not point to a significant safety signal in these areas. Importantly, large cardiovascular outcome trials conducted in patients with type 2 diabetes have shown that GLP-1RAs can reduce the incidence of major adverse cardiovascular events. This suggests that their benefits extend beyond weight reduction alone, although further research is needed to confirm whether these advantages also apply to obese patients without diabetes [14].

Clinical and Public Health Implications

The growing availability of GLP-1RAs provides clinicians with a powerful and innovative tool for addressing obesity. Nonetheless, several barriers to widespread adoption persist. The most pressing issue is the high cost of therapy, which may significantly limit patient access within many healthcare systems worldwide. Additionally, treatment requires subcutaneous injections, a factor that may reduce patient acceptance compared with more convenient oral therapies. Despite these obstacles, the potential of GLP-1RAs to substantially reduce obesity-related comorbidities and to lower healthcare costs in the long term presents a strong argument in favor of their broader clinical implementation. If incorporated appropriately, these therapies could play a major role in reducing the global burden of obesity [14].

Future Directions

Looking forward, ongoing research continues to investigate the promise of next-generation incretin-based therapies. Dual and triple receptor agonists targeting GLP-1, GIP, and glucagon receptors are being actively studied, with early data suggesting even greater efficacy and potentially wider metabolic benefits than those achieved by current treatments. In addition to novel agents, combined treatment strategies that integrate pharmacological therapy with structured behavioral and lifestyle interventions may offer further improvements in clinical outcomes. Future research must also address unresolved questions, including the sustainability of weight loss over extended periods, the optimal duration of therapy, and how best to balance efficacy, long-term safety, and cost-effectiveness. These insights will be crucial for guiding clinical decision-making and for ensuring that GLP-1RAs and their successors are utilized in the most effective and equitable manner [15].

Conclusions

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have fundamentally reshaped the therapeutic approach to obesity, establishing themselves as one of the most significant pharmacological innovations of recent decades. Data obtained from multiple large-scale randomized controlled trials consistently confirm their ability to produce weight loss that is not only statistically significant but also clinically meaningful, with effects that can be maintained over extended periods of time. Importantly, these benefits are not limited to body weight reduction alone. Treatment with GLP-1RAs has also been associated with improvements in glycemic control, reductions in blood pressure, and favorable changes in lipid metabolism, thereby addressing several of the key cardiometabolic risk factors that contribute to obesity-related morbidity and mortality. Among the currently available agents, semaglutide has demonstrated the most pronounced reductions in body weight, while emerging data on tirzepatide point toward an even higher degree of efficacy, with outcomes that approach those traditionally associated with bariatric surgical procedures [16].

Despite the impressive advances achieved with these agents, certain challenges remain unresolved and highlight areas requiring further attention. One of the most significant concerns is weight regain following the discontinuation of therapy, a finding that underscores the chronic and relapsing nature of obesity. This observation reinforces the need to view GLP-1RAs as long-term, possibly lifelong, treatment options rather than short-term interventions. With regard to safety, adverse events are in most cases gastrointestinal and manageable; however, continuous monitoring and post-marketing surveillance are essential in order to establish the long-term safety profile of these drugs, particularly in non-diabetic populations. In addition, economic barriers such as high treatment costs, together with limited availability in many healthcare systems, may restrict access to therapy, particularly in regions with constrained medical resources.

In conclusion, GLP-1RAs represent a paradigm shift in the medical management of obesity, offering levels of efficacy and additional metabolic benefits that were previously unattainable with pharmacological therapy alone. The future of research in this field should therefore concentrate on optimizing strategies for long-term treatment, investigating the potential of next-generation incretin therapies, and developing approaches that address issues of cost, access, and equity in healthcare delivery. By integrating these pharmacological tools with evidence-based lifestyle modifications and behavioral interventions, clinicians may help patients achieve not only sustained improvements in weight management but also meaningful reductions in the overall burden of obesity-related disease worldwide [17].

Disclosures

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Supervision: Natalia Strumnik.

All authors have read and agreed with the published version of the manuscript.

Funding statement: Not applicable.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability: Not applicable.

Acknowledgments: Not applicable.

Conflict or interest statement: Authors declare no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process:

During preparing this work the authors have used ChatGPT for the purpose of improving language and readability. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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