QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

KOPNIAK, Weronika, KONOPKO, Sebastian, GÓRA, Katarzyna, WASILEWSKA, Wiktoria, BUSZTA, Blanka, KOKUSZKO, Inga and MARKIEWICZ, Mateusz. Tirzepatide and semaglutide in obesity management and their impact on health-related quality of life – a comparative narrative review. Quality in Sport. 2026;67:74311. https://doi.org/10.12775/QS.2026.67.74311

ARTICLE TIMELINE
Received: 14.07.2026. Revised: 02.08.2026. Accepted: 02.08.2026. Published: 10.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Tirzepatide and semaglutide in obesity management and their impact on health-related quality of life – a comparative narrative review

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Abstract

Background. Obesity is a chronic, relapsing disease associated with increased morbidity, mortality, and reduced health-related quality of life (HRQoL). Recent advances in incretin-based pharmacotherapy, including semaglutide and tirzepatide, show substantial efficacy in weight management.

Aim. This study compared the efficacy, weight loss durability, HRQoL impact, and safety profiles of semaglutide and tirzepatide based on pivotal phase 3 trials.

Material and methods. We conducted a comparative narrative review. A structured literature search of PubMed and ClinicalTrials.gov identified randomized controlled trials evaluating semaglutide and tirzepatide in adults with overweight or obesity without type 2 diabetes. The analysis focused on phase 3 trials from the STEP (1, 3, 4) and SURMOUNT (1, 3, 4) clinical programs. Outcomes included percentage weight reduction, achievement of clinically significant thresholds, maintenance of weight loss, HRQoL changes, and safety.

Results. Both agents resulted in significant weight reduction versus placebo, with greater effects observed for tirzepatide, particularly at higher doses. A higher proportion of participants achieved ≥10%, ≥15%, and ≥20% weight loss with tirzepatide. Improvements in HRQoL were observed with both treatments, specifically in physical functioning domains. Weight regain occurred following treatment discontinuation, while continued therapy was associated with sustained or further weight loss. Gastrointestinal adverse events were the most commonly reported; overall safety profiles were consistent with incretin-based therapies.

Conclusions. Semaglutide and tirzepatide are highly effective pharmacological treatments for obesity, with tirzepatide demonstrating superior weight loss efficacy. Sustained treatment is essential for long-term weight management. These therapies represent a significant advancement in treatment, although differences in study design should be considered when interpreting comparative outcomes.

Key words: obesity, semaglutide, tirzepatide, weight loss, incretin therapy, quality of life.

1. Introduction

According to the World Health Organization (WHO), obesity is defined as a body mass index (BMI; weight (kg)/height (m)²) of 30 or above in adults [1]. Obesity is a major risk factor for multiple chronic diseases, including type 2 diabetes, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), myocardial infarction, obstructive sleep apnoea, osteoarthritis, mental disorders, and certain types of cancer [2].

Even in the absence of overt complications, obesity is associated with a reduction in quality of life. Individuals with obesity demonstrate poorer physical and mental functioning compared to those with normal body weight [3]. According to epidemiological data, over 1 billion people were classified as obese in 2022 [4]. This makes obesity one of the most significant global public health challenges.

Due to the increasing prevalence of obesity, effective treatment strategies are essential. Traditional methods of obesity management include behavioral interventions and pharmacotherapy. Behavioral interventions, understood as dietary modification and increased physical activity, result in an average long-term weight loss of approximately 5%; however, maintaining this effect remains challenging [5].

In the pharmacotherapy of obesity, the following agents are used: orlistat, phentermine–topiramate, naltrexone–bupropion and liraglutide. The effectiveness of orlistat is relatively modest compared to other pharmacological agents. Phentermine–topiramate and liraglutide are the most effective treatments; however, their effectiveness is approximately 8–9% and 6–7% reduction in body weight, respectively. These therapies are associated with adverse effects, which may limit their use [6,7].

Therefore, new pharmacological methods for obesity treatment have been sought. In recent years, semaglutide and tirzepatide have emerged as promising therapeutic options, not only in terms of weight reduction but also potential improvement in health-related quality of life.

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is an intestinal incretin hormone that exerts anorectic effects both centrally and peripherally by increasing satiety and delaying gastric emptying. Semaglutide primarily reduces energy intake rather than increasing energy expenditure. Although the exact mechanisms are not fully

understood, it is thought to act on hypothalamic pathways involved in appetite regulation. Additionally, it slows gastric emptying [8].

Tirzepatide, similarly to semaglutide, acts as a GLP-1 receptor agonist; however, unlike semaglutide, it also acts as a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, making it a dual incretin receptor agonist. Similar to semaglutide, tirzepatide reduces appetite through central mechanisms and improves satiety, while delayed gastric emptying is primarily mediated via GLP-1 receptor activation. The additional activation of GIP receptors may contribute to enhanced metabolic effects and greater weight reduction [9].

Semaglutide and tirzepatide represent a significant advancement in the treatment of obesity. Comparing the efficacy of these drugs and their impact on quality of life is essential for optimizing therapy. The aim of this review is to evaluate and compare their effectiveness and influence on Health-related quality of life.

2. Methods

2.1 Study design and data sources

This study was conducted as a comparative narrative review aimed at evaluating and contrasting the efficacy, durability of weight loss, health-related quality of life (HRQoL), and safety profiles of semaglutide and tirzepatide in the management of obesity.

A structured literature search was performed using PubMed and ClinicalTrials.gov to identify relevant randomized controlled trials (RCTs). The search included studies published up to 2026 and used combinations of the following keywords: “semaglutide”, “tirzepatide”, “obesity”, “overweight”, “weight loss”, “STEP trials”, “SURMOUNT trials”, “randomized controlled trial”, and “quality of life”.

Particular emphasis was placed on pivotal phase 3 trials from the STEP (semaglutide) and SURMOUNT (tirzepatide) clinical development programs, specifically STEP 1, STEP 3,

STEP 4, and SURMOUNT-1, SURMOUNT-3, and SURMOUNT-4, due to their methodological quality, large sample sizes, and direct relevance to obesity pharmacotherapy.

2.2 Study selection criteria

Studies were included if they met the following criteria:

(1)randomized controlled trial design;

(2) adult population with obesity (BMI ≥30 kg/m²) or overweight (BMI ≥27 kg/m²) with weight-related comorbidities, excluding populations with type 2 diabetes;

(3) evaluation of semaglutide or tirzepatide as pharmacological interventions;

(4) reporting at least one relevant outcome, including weight reduction, weight loss thresholds, maintenance of weight loss, HRQoL, or safety.

Studies were excluded if they involved paediatric populations, observational studies, non-randomized trials, or did not report clinically relevant weight-related outcomes.

2.3 Study selection and data extraction

Titles and abstracts identified through the literature search were screened for relevance. Full-text articles of potentially eligible studies were subsequently reviewed. Data were extracted manually and included study characteristics (sample size, intervention, comparator, and duration), study design features (including lifestyle interventions and run-in periods), and reported outcomes.

Given the comparative nature of this review, particular attention was paid to differences in study design between the STEP and SURMOUNT trials, including the use of intensive lifestyle interventions (e.g., STEP 3 and SURMOUNT-3) and withdrawal or maintenance phases (STEP 4 and SURMOUNT-4).

2.4 Outcomes

The primary outcome of this review was percentage change in body weight from baseline.

Secondary outcomes included:

- proportion of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss,
- maintenance of weight loss following continuation or discontinuation of therapy,
- changes in HRQoL measured using validated instruments, including the Short Form-36 (SF-36) and the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT),
- safety and tolerability, including gastrointestinal adverse events and serious adverse events,
- the impact of combined pharmacological and lifestyle interventions.

Due to heterogeneity in study design and outcome reporting, no formal meta-analysis was performed, and results were synthesized descriptively.

2.5 AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data

processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Results.

The main characteristics of the included trials are summarized in Table 1.

Table 1. Characteristics of included STEP and SURMOUNT trials

Trial	Drug	Population	Sample size (n)	Intervention	Comparator	Duration	Key study design features
STEP 1	Sema 2,4mg	Obesity/OW + ≥1 WR comorb., no T2D	1961	Sema + lifestyle	Placebo + lifestyle	68 w	RCT, DB, PC
STEP 3	Sema 2,4mg	Obesity/OW + ≥1 WR comorb., no T2D	611	Sema + IBT (VLCD)	Placebo + IBT	68 w	RCT
STEP 4	Sema 2,4mg	Obesity/OW + ≥1 WR comorb., no T2D	803	Continued sema	Switch to placebo	68 w (20 RI+48 RP)	Withdrawal RCT
SURMOUNT-1	Tirz 5-15mg	Obesity/OW + ≥1 WR comorb., no T2D	2539	Tirz + lifestyle	Placebo + lifestyle	72 w	RCT, DB, PC
SURMOUNT-3	Tirz 10-15mg	Obesity/OW + ≥1 WR comorb., no T2D	579	Tirz following IBT-inducted ≥5% WL	Placebo following IBT-inducted ≥5% WL	72 w	RCT
SURMOUNT-4	Tirz 10-15mg	Obesity/OW + ≥1 WR comorb., no T2D	783	Continued tirz	Switch to placebo	88 w (36 RI+52 RP)	Withdrawal RCT

Source: own elaboration

Abbreviations: Sema, semaglutide; Tirz, tirzepatide; OW, overweight; WR comorb., weight-related comorbidity; T2D, type 2 diabetes; IBT, intensive behavioral therapy; VLCD, very-low-calorie diet; WL, weight loss; RI, run-in chase; RP, randomized chase; RCT, randomized controlled trial; DB, double-blind; PC, placebo-controlled.

3.1. Effects on Body Weight Reduction

In the STEP 1 and STEP 3 trials, semaglutide resulted in a mean body weight reduction of 14.9% (STEP 1) to 16.0% (STEP 3), compared with 2.4% and 5.7% in the respective placebo groups [10,11]. In the SURMOUNT-1 trial, tirzepatide achieved greater mean reductions, ranging from 15.0% with 5 mg to 20.9% with 15 mg, compared with 3.1% in the placebo group. In SURMOUNT-3, additional weight reduction of 18.4% was observed with tirzepatide, compared with 2.5% in the placebo arm [12,13].

The STEP 1 and STEP 3 trials also evaluated the proportion of participants achieving clinically significant weight loss thresholds. In the semaglutide group, 86.4–86.6% of participants achieved ≥5% weight loss**,** 69.1–75.3% achieved ≥10%**,** 50.5–55.8% achieved ≥15%**,** and 32.0–35.7% achieved ≥20% weight reduction**.** In contrast, lower proportions were observed in the placebo group, with 31.5–47.6%**,** 12.0–27.0%**,** 4.9–13.2%**,** and 1.7–3.7% of participants reaching the respective thresholds [10,11]. Comparable outcomes were observed in the SURMOUNT trials. In the SURMOUNT-1, the proportion of participants achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss ranged from 85.1-90.9%, 68.5-83.5%, 48.0-70.6% and 30.0-56.7% respectively, depending on the trizepatide dose (5-15mg), compared with 34.5%, 18.0%, 8.8% and 3.1% in the placebo group. In SURMOUNT-3, the respective thresholds where achieved by 87.5%, 76.7%, 65.4% and 44.7% of participants treated with tirzepatide, compared with 16.5%, 8.9%, 4.2% and 2.2% in the placebo group [12,13].

3.2. Maintenance of Weight Loss

Both STEP 4 and SURMOUNT-4 trials evaluated the maintenance of weight loss following initial treatment with semaglutide and tirzepatide, respectively.

During the run-in period, mean body weight decreased by 10.6% in the semaglutide group and by 20.9% in the tirzepatide group. After randomization, continued treatment with semaglutide resulted in an additional mean weight reduction of 7.9%, whereas participants

switched to placebo experienced a weight regain of 6.9%. Overall, total weight loss at the end of the study was 17.4% in the semaglutide group compared with 5.0% in the placebo group [14].

A similar pattern was observed in the SURMOUNT-4 trial. Continued treatment with tirzepatide led to an additional mean weight reduction of 5.5%, while participants switched to placebo experienced a weight regain of 14.0%. At the end of the study, the total weight reduction was 25.8% in the tirzepatide group, compared with 9.5% in the placebo group [15].

3.3. Health-related Quality of Life (HRQoL)

Health-related quality of life (HRQoL) in the STEP trials was assessed using validated instruments, including the 36 Items Short Form Health Survey (SF-36) and the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT), with particular emphasis on physical and mental components.

In the STEP 1 and STEP 3 trials, semaglutide was associated with greater improvements in HRQoL compared with placebo. Improvements in the SF-36 physical functioning score ranged from 2.21 to 2.4 in the semaglutide group, compared with 0.41 to 1.6 in the placebo group. In STEP 3, improvements in the physical and mental component scores were 3.0 and −0.8, respectively, compared with 2.3 and −2.9 in the placebo group. Similarly, in STEP 1, the IWQOL-Lite-CT total score improved by 14.67 points in the semaglutide group, compared with 5.25 points in the placebo group [10,11]. For tirzepatide, improvements in SF-36 scores ranged from 3.3 to 3.6, compared with −0.6 to 1.7 for placebo in the SURMOUNT-1 and SURMOUNT-3 trials. In the SURMOUNT-3 trial, tirzepatide improvement in the IWQOL-Lite-CT score was 13.9 compared with 1.1 for placebo [12,13]

After discontinuation of semaglutide in STEP 4, HRQoL scores decreased, with a reduction of 1.5 points in the overall SF-36 score, including 0.9 in the physical component and 3.4 in the mental component, compared with an increase of 1.0 in the group continuing

semaglutide (0.8 in the physical component and 0.1 in the mental component). Comparable outcomes were observed in the SURMOUNT-4 trial. In the group continuing treatment with tirzepatide, SF-36 increased in the physical functioning domain (PFD) by 0.8 and in the mental health domain (MHD) by 0.3, while the IWQOL-Lite-CT physical function composite score increased by 4.3, compared with decreases of −1.8, −2.1, and −5.1, respectively, in the placebo group. However, over the entire SURMOUNT-4 trial period, the increase in the SF-36 index was 6.4 for PFD and 2.4 for MHD, and the IWQOL-Lite-CT physical function composite score increased by 26, compared with 3.7, 0.2, and 16.7, respectively, in the placebo group [14,15].

3.4. Adverse Events

Adverse events in the STEP and SURMOUNT trials were primarily gastrointestinal in nature and were generally consistent with the known safety profiles of incretin-based therapies. The most frequently reported events included nausea, diarrhoea, vomiting, and constipation.

In the STEP 1 and STEP 3 trials, gastrointestinal adverse events were more commonly observed in the semaglutide group compared with placebo (74.2-82.8% vs. 47.9-63.2%). These events were typically mild to moderate in severity and occurred predominantly during the dose-escalation phase. Discontinuation rates due to adverse events were higher in the semaglutide group than in the placebo group (5.9-7.0% vs. 2.9-3.1%) [10,11]. Similarly, in the SURMOUNT-1 and SURMOUNT-3 trials, tirzepatide was associated with a higher incidence of gastrointestinal adverse events compared with placebo. Unlike the STEP trials, adverse events were reported as individual symptoms rather than as a combined category. The most commonly reported events included nausea, diarrhoea, vomiting, and constipation, with a higher frequency observed at higher doses of tirzepatide. Most adverse events were mild to moderate and occurred during the early phase of treatment. Discontinuation rates due to

adverse events were 4.3-10.5% in the tirzepatide group compared with 2.1-2.6% in the placebo group.

Serious adverse events were infrequent across STEP 1, STEP 3, SURMOUNT-1, and SURMOUNT-3 trials and occurred at comparable rates between active treatment and placebo groups (semaglutide: 9.1–9.8% vs. 2.9–6.4%; tirzepatide: 5.1–6.9% vs. 4.8–6.8%) [12,13].

In the STEP 4 and SURMOUNT-4 trials, overall safety profiles remained consistent with those observed in earlier phases of treatment. No new safety signals were identified during the maintenance periods, and adverse event patterns were comparable between continued active treatment and placebo withdrawal groups [14,15].

A summary of the key efficacy and maintenance outcomes is presented in Table 2.

Table 2. Comparative clinical outcomes of semaglutide and tirzepatide across STEP and SURMOUNT trials

Outcome	**Semaglutide (STEP 1, 3, 4)**	**Tirzepatide (SURMOUNT-1, 3, 4)**
Mean WL (%)	14.9–16.0%	15.0–20.9%
≥5% WL	86.4–86.6%	85.1–90.9%
≥10% WL	69.1–75.3%	68.5–83.5%
≥15% WL	50.5–55.8%	48.0–70.6%
≥20% WL	32.0–35.7%	30.0–56.7%
Maintenance (continued tx)	−7.9% vs. +6.9% placebo	−5.5% vs. +14.0% placebo
Total WL (maintenance trials)	17.4% vs. 5.0% placebo	25.8% vs. 9.5% placebo
HRQoL (SF-36 PCS)	+2.2–3.0	+3.3–3.6
HRQoL (IWQOL-Lite-CT)	+14.7	+13.9
GI adverse events	74.2–82.8%	Reported as individual symptoms*
Discontinuation due to AE	5.9–7.0%	4.3–10.5%
Serious AE	9.1–9.8% vs. 2.9–6.4% placebo	9.1–9.8% vs. 2.9–6.4% (placebo)

Source: own elaboration

Notes: * In SURMOUNT trials, gastrointestinal adverse events were reported as individual symptoms (e.g., nausea, diarrhoea, vomiting, constipation) rather than as a combined category. Abbreviations: WL, weight loss; tx, treatment; HRQoL, health-related quality of life; PCS, physical component score; GI, gastrointestinal; AE, adverse events.

4. Discussion

The present narrative review summarizes the efficacy and safety of semaglutide and tirzepatide based on key STEP and SURMOUNT trials, demonstrating that both agents produce substantial and clinically meaningful reductions in body weight in individuals with obesity or overweight without type 2 diabetes [10–15].

4.1. Interpretation of weight loss outcomes

Both semaglutide and tirzepatide achieved significant weight reduction compared with placebo; however, tirzepatide consistently demonstrated greater efficacy, with weight loss reaching up to approximately 20% depending on the dose [12,13]. In contrast, semaglutide resulted in reductions of approximately 15–16% in comparable populations [10,11]. These findings suggest a greater magnitude of weight loss with tirzepatide.

The greater efficacy of tirzepatide may be explained by its dual agonism of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, resulting in complementary and potentially synergistic metabolic effects compared with GLP-1 receptor agonism alone [16]. Importantly, the proportion of participants achieving clinically meaningful weight loss thresholds (≥5%, ≥10%, ≥15%, and ≥20%) was high for both agents, further supporting their effectiveness [10–13]. Greater weight reduction is associated with progressive improvements in cardiometabolic risk factors, with more pronounced benefits observed at higher levels of weight loss [17].

4.2. Maintenance of weight loss and chronic disease perspective

Findings from STEP 4 and SURMOUNT-4 highlight the importance of continued treatment in maintaining weight loss. Discontinuation of therapy was associated with weight

regain, whereas ongoing pharmacotherapy led to further reductions or stabilization of body weight [14,15].

These observations support the concept of obesity as a chronic, relapsing disease requiring long-term management rather than short-term intervention. The weight regain observed following treatment withdrawal is consistent with physiological adaptations favouring increased appetite and energy conservation [18].

4.3. Impact on health-related quality of life

Both semaglutide and tirzepatide were associated with improvements in health-related quality of life, particularly in physical functioning domains [10–13]. Improvements in SF-36 and IWQOL-Lite-CT scores indicate that weight reduction achieved with these therapies translates into meaningful benefits in daily functioning and patient well-being.

Improvements were more pronounced in physical components than in mental health domains, suggesting that physical health improvements are the primary driver of HRQoL benefits [10,11].

4.4. Safety and tolerability

The safety profiles of semaglutide and tirzepatide were generally consistent with those of incretin-based therapies. Gastrointestinal adverse events, including nausea, diarrhoea, vomiting, and constipation, were the most commonly reported and were typically mild to moderate in severity. These events occurred predominantly during the dose-escalation phase and tended to decrease over time.

Although gastrointestinal adverse events were more frequent with active treatment compared with placebo, discontinuation rates due to adverse events remained relatively low, suggesting overall acceptable tolerability [10–13].

Serious adverse events were infrequent and occurred at comparable rates between active treatment and placebo groups in the core trials [12,13]. Furthermore, maintenance trials

did not identify new safety signals, supporting the consistency of the safety profile over longer treatment durations [14,15].

4.5. Clinical implications

The magnitude of weight loss observed with semaglutide and particularly tirzepatide represents a substantial advancement in the pharmacological management of obesity [10–13]. The degree of weight reduction achieved approaches that observed after bariatric surgery in long-term meta-analyses [19]. These therapies may be particularly beneficial for patients with obesity-related comorbidities, as weight reduction of this magnitude is associated with improvements in metabolic health, while broader reductions in cardiovascular risk factors and morbidity have been demonstrated in obesity-related cardiometabolic studies [17,20].

4.6. Limitations

This review has several limitations. First, it is based on a limited number of randomized controlled trials with relatively homogeneous populations, which may limit generalizability to broader real-world settings. Second, differences in study design, including lifestyle interventions and withdrawal phases, may complicate direct comparisons between trials [10–15]. Third, long-term data beyond trial duration remain limited.

Additionally, the design of the SURMOUNT-3 trial, which included a run-in period of intensive lifestyle intervention with inclusion restricted to participants achieving at least 5% weight loss, may have introduced selection bias toward individuals more responsive to weight loss interventions. This enrichment design may limit generalizability and potentially overestimate treatment effects compared with an unselected real-world population.

4.7. Future directions

Future research should focus on long-term outcomes, including cardiovascular endpoints, durability of weight loss, and real-world effectiveness [20]. Additionally, incretin-based therapies may further enhance weight loss outcomes, with dual agonists such as

tirzepatide representing the current therapeutic advancement and emerging triple agonists such as retatrutide potentially offering even greater efficacy in future clinical practice [16,21].

5. Conclusions

Semaglutide and tirzepatide represent highly effective pharmacological options for the management of obesity, demonstrating substantial and clinically meaningful weight reduction across the STEP and SURMOUNT clinical trial programs. Comparative analysis indicates that tirzepatide may achieve greater weight loss, particularly at higher doses, while both agents are associated with improvements in health-related quality of life and generally acceptable safety profiles.

The durability of weight loss appears to depend on continued treatment, as demonstrated in withdrawal studies, highlighting the chronic and relapsing nature of obesity and the need for sustained therapeutic strategies. Differences in study design, including the use of intensive lifestyle interventions and study designs that may preferentially include participants more responsive to treatment, should be considered when interpreting comparative efficacy between trials.

Incretin-based therapies are reshaping the treatment paradigm for obesity. Future research should focus on long-term outcomes, including cardiovascular endpoints and real-world effectiveness, as well as the development of next-generation agents, such as multi-receptor agonists, which may further enhance therapeutic outcomes.

Declarations

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

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This study was based exclusively on previously published scientific literature and did not involve human participants or animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: The authors would like to thank all researchers whose studies contributed to the development of this narrative review.

Conflicts of Interest: The authors deny any conflict of interest.

References

1. World Health Organization. (2023). Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Blüher M. (2025). An overview of obesity-related complications: The epidemiological evidence linking body weight and other markers of obesity to adverse health outcomes. Diabetes, obesity & metabolism, 27 Suppl 2(Suppl 2), 3–19. https://doi.org/10.1111/dom.16263

3. Ul-Haq, Z., Mackay, D. F., Fenwick, E., & Pell, J. P. (2013). Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. Obesity (Silver Spring, Md.), 21(3), E322–E327. https://doi.org/10.1002/oby.20107

4. Ahmed, S. K., & Mohammed, R. A. (2025). Obesity: Prevalence, causes, consequences, management, preventive strategies and future research directions. Metabolism open, 27, 100375. https://doi.org/10.1016/j.metop.2025.100375

5. Look AHEAD Research Group (2014). Eight-year weight losses with an intensive lifestyle intervention: the look AHEAD study. Obesity (Silver Spring, Md.), 22(1), 5–13. https://doi.org/10.1002/oby.20662

6. Shi, Q., Wang, Y., Hao, Q., Vandvik, P. O., Guyatt, G., Li, J., Chen, Z., Xu, S., Shen, Y., Ge, L., Sun, F., Li, L., Yu, J., Nong, K., Zou, X., Zhu, S., Wang, C., Zhang, S., Qiao, Z., Jian, Z., … Li, S. (2024). Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet (London, England), 403(10434), e21–e31. https://doi.org/10.1016/S0140-6736(24)00351-9

7. McGowan, B., Ciudin, A., Baker, J. L., Busetto, L., Dicker, D., Frühbeck, G., Goossens, G. H., Monami, M., Sbraccia, P., Martinez-Tellez, B., Woodward, E., & Yumuk, V. (2025). A systematic review and meta-analysis of the efficacy and safety of pharmacological treatments for obesity in adults. Nature medicine, 31(10), 3317–3329. https://doi.org/10.1038/s41591-025-03978-z

8. Mahapatra, M. K., Karuppasamy, M., & Sahoo, B. M. (2022). Therapeutic Potential of Semaglutide, a Newer GLP-1 Receptor Agonist, in Abating Obesity, Non-Alcoholic Steatohepatitis and Neurodegenerative diseases: A Narrative Review. Pharmaceutical research, 39(6), 1233–1248. https://doi.org/10.1007/s11095-022-03302-1

9. Galindo, R. J., Cheng, A. Y. Y., Longuet, C., Ai, M., Coskun, T., Malik, R., Peleshok, J., Levine, J. A., & Dunn, J. P. (2026). Insights into the Mechanism of Action of Tirzepatide: A Narrative Review. Diabetes therapy : research, treatment and education of diabetes and related disorders, 17(1), 19–40. https://doi.org/10.1007/s13300-025-01804-w

10. Wilding, J. P. H., Batterham, R. L., Calanna, S., Davies, M., Van Gaal, L. F., Lingvay, I., McGowan, B. M., Rosenstock, J., Tran, M. T. D., Wadden, T. A., Wharton, S., Yokote, K., Zeuthen, N., Kushner, R. F., & STEP 1 Study Group (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity. The New England journal of medicine, 384(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183

11. Wadden, T. A., Bailey, T. S., Billings, L. K., Davies, M., Frias, J. P., Koroleva, A., Lingvay, I., O'Neil, P. M., Rubino, D. M., Skovgaard, D., Wallenstein, S. O. R., Garvey, W. T., & STEP 3 Investigators (2021). Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA, 325(14), 1403–1413. https://doi.org/10.1001/jama.2021.1831

12. Jastreboff, A. M., Aronne, L. J., Ahmad, N. N., Wharton, S., Connery, L., Alves, B., Kiyosue, A., Zhang, S., Liu, B., Bunck, M. C., Stefanski, A., & SURMOUNT-1 Investigators (2022). Tirzepatide Once Weekly for the Treatment of Obesity. The New England journal of medicine, 387(3), 205–216. https://doi.org/10.1056/NEJMoa2206038

13. Wadden, T. A., Chao, A. M., Machineni, S., Kushner, R., Ard, J., Srivastava, G., Halpern, B., Zhang, S., Chen, J., Bunck, M. C., Ahmad, N. N., & Forrester, T. (2023). Tirzepatide after

intensive lifestyle intervention in adults with overweight or obesity: the SURMOUNT-3 phase 3 trial. Nature medicine, 29(11), 2909–2918. https://doi.org/10.1038/s41591-023-02597-w

14. Rubino, D., Abrahamsson, N., Davies, M., Hesse, D., Greenway, F. L., Jensen, C., Lingvay, I., Mosenzon, O., Rosenstock, J., Rubio, M. A., Rudofsky, G., Tadayon, S., Wadden, T. A., Dicker, D., & STEP 4 Investigators (2021). Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA, 325(14), 1414–1425. https://doi.org/10.1001/jama.2021.3224

15. Aronne, L. J., Sattar, N., Horn, D. B., Bays, H. E., Wharton, S., Lin, W. Y., Ahmad, N. N., Zhang, S., Liao, R., Bunck, M. C., Jouravskaya, I., Murphy, M. A., & SURMOUNT-4 Investigators (2024). Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity: The SURMOUNT-4 Randomized Clinical Trial. JAMA, 331(1), 38–48. https://doi.org/10.1001/jama.2023.24945

16. Willard, F. S., Douros, J. D., Gabe, M. B., Showalter, A. D., Wainscott, D. B., Suter, T. M., Capozzi, M. E., van der Velden, W. J., Stutsman, C., Cardona, G. R., Urva, S., Emmerson, P. J., Holst, J. J., D'Alessio, D. A., Coghlan, M. P., Rosenkilde, M. M., Campbell, J. E., & Sloop, K. W. (2020). Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI insight, 5(17), e140532. https://doi.org/10.1172/jci.insight.140532

17. Busetto, L., Dicker, D., Frühbeck, G., Halford, J. C. G., Sbraccia, P., Yumuk, V., & Goossens, G. H. (2024). A new framework for the diagnosis, staging and management of obesity in adults. Nature medicine, 30(9), 2395–2399. https://doi.org/10.1038/s41591-024-03095-3

18. Bray, G. A., Kim, K. K., Wilding, J. P. H., & World Obesity Federation (2017). Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity

Federation. Obesity reviews : an official journal of the International Association for the Study of Obesity, 18(7), 715–723. https://doi.org/10.1111/obr.12551

19. O'Brien, P. E., Hindle, A., Brennan, L., Skinner, S., Burton, P., Smith, A., Crosthwaite, G., & Brown, W. (2019). Long-Term Outcomes After Bariatric Surgery: a Systematic Review and Meta-analysis of Weight Loss at 10 or More Years for All Bariatric Procedures and a Single-Centre Review of 20-Year Outcomes After Adjustable Gastric Banding. Obesity surgery, 29(1), 3–14. https://doi.org/10.1007/s11695-018-3525-0

20. Powell-Wiley, T. M., Poirier, P., Burke, L. E., Després, J. P., Gordon-Larsen, P., Lavie, C. J., Lear, S. A., Ndumele, C. E., Neeland, I. J., Sanders, P., St-Onge, M. P., & American Heart Association Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Stroke Council (2021). Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation, 143(21), e984-e1010. https://doi.org/10.1161/CIR.0000000000000973

21. Jastreboff, A. M., Kaplan, L. M., Frías, J. P., Wu, Q., Du, Y., Gurbuz, S., Coskun, T., Haupt, A., Milicevic, Z., Hartman, M. L., & Retatrutide Phase 2 Obesity Trial Investigators (2023). Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. The New England journal of medicine, 389(6), 514–526. https://doi.org/10.1056/NEJMoa2301972