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GLP-1 Agonists and Dual Agonists in Obesity Treatment: Benefits, Risks, and Clinical Challenges in Geriatric Patients

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ABSTRACT

Introduction. The global prevalence of obesity has increased markedly in recent decades, becoming a major contributor to metabolic syndrome (MetS), cardiovascular disease, and mortality. This trend increasingly affects older adults, in whom obesity often coexists with sarcopenia, frailty, and multimorbidity. Novel pharmacological therapies, particularly glucagon-like peptide-1 (GLP-1) receptor agonists and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, have demonstrated unprecedented efficacy in weight reduction, yet data in geriatric populations remain limited.

Aim. To evaluate the efficacy and safety of GLP-1 receptor agonists and dual GLP-1/GIP agonists in the treatment of obesity and MetS, with a particular focus on adults aged ≥65 years.

Materials and Methods. A systematic literature search of PubMed, Embase, and Scopus was conducted for studies published between 2020 and 2025. Phase 2–3 randomized controlled trials and real-world observational studies evaluating semaglutide and tirzepatide were included. Outcomes assessed comprised weight loss, cardiometabolic effects, adverse events, and data relevant to older adults, including body composition and treatment discontinuation.

Results. Both semaglutide and tirzepatide produced substantial and sustained weight loss, with mean reductions ranging from approximately 15% to over 20%, and significant improvements in glycemic control, lipid profile, and blood pressure. Tirzepatide consistently achieved greater weight reduction than semaglutide. Limited subgroup and post hoc analyses suggest that older adults experience meaningful metabolic benefits, although higher rates of gastrointestinal adverse events and treatment discontinuation have been reported.

Discussion. In older patients, pharmacologically induced weight loss may be accompanied by disproportionate loss of lean body mass, increasing the risk of sarcopenia, frailty, and functional decline. Without appropriate nutritional and exercise interventions, these risks may attenuate the cardiometabolic benefits of treatment.

Conclusions. GLP-1 and dual GLP-1/GIP receptor agonists are highly effective therapies for obesity, including in older adults, but require individualized risk–benefit assessment.

Integration with nutritional support and resistance training is essential. Dedicated geriatric-focused trials evaluating functional outcomes and long-term safety are urgently needed.
Keywords: obesity, metabolic syndrome, older adults, dual GIP/GLP-1 agonists, semaglutide, tirzepatide, sarcopenic obesity

Introduction

The prevalence of obesity has risen dramatically, emerging as a major public health challenge worldwide. According to the 2025 World Obesity Atlas, published on World Obesity Day (4 March), the total number of adults living with obesity is projected to increase by more than 115% between 2010 and 2030, rising from 524 million to 1.13 billion [1].

According to a comprehensive analysis by the NCD Risk Factor Collaboration (2024), which utilized data from over 3,600 population-based studies involving 222 million participants, the combined prevalence of underweight and obesity increased in most nations between 1990 and 2022, specifically in 162 countries (81%) for women and 140 countries (70%) for men. This epidemiological transition reflects a fundamental shift from underweight to obesity dominance. While underweight prevalence has declined, the overall burden of excess body weight is now increasingly driven by rising obesity rates. By 2022, the probability that obesity prevalence exceeded underweight prevalence was at least 0.80 in 177 countries (89%) for women and 145 countries (73%) for men [2].

Obesity among elderly has mirrored trends observed in the general population. In the United States, for instance, approximately 37.1% of men and 33.6% of women aged 60 years and older are classified as having obesity (BMI ≥ 30 kg/m^2) [3].

The increasing incidence of obesity has profound implications for metabolic health, as excess adiposity is a central driver of metabolic syndrome (MetS). Metabolic syndrome is defined by the presence of at least three of five specific risk factors: abdominal obesity, elevated fasting glucose, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein (HDL) cholesterol [4]. According to a systematic review and analysis of data spanning 2000 to 2023,

the global occurrence of MetS in adults increased from 11.9% in 2000 to 28.4% in 2023. This surge represents an absolute increase of 16.5%, indicating that as of 2023, approximately 1.54 billion adults worldwide were living with the syndrome [5]. MetS is associated with substantially elevated health risks, including a 5-fold higher likelihood of developing type 2 diabetes, a 2-fold higher risk of coronary heart disease and cerebrovascular events, and a 1.5-fold increase in all-cause mortality, highlighting its critical role as a predictor of major chronic diseases [6].

In the elderly population, adiposity is frequently accompanied by a progressive loss of muscle mass and strength, a condition known as sarcopenic obesity. This phenomenon, characterized by the coexistence of excess adipose tissue with age-related declines in skeletal muscle mass, strength, and function, is increasingly recognized as a major public health concern due to its its association with compounded adverse outcomes in older adults, including cardiovascular disease, metabolic disorders and elevated mortality compared with either obesity or sarcopenia individually [7]. Targeted strategies are therefore essential to prevent or mitigate these adverse outcomes.

The rapidly increasing prevalence of obesity and MetS has highlighted an urgent need for effective interventions, including growing pressure to implement pharmacological therapies capable of achieving clinically meaningful and sustained weight reduction. In this context, glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor agonists have emerged as highly promising pharmacological treatments for obesity [8]. The STEP-1 clinical trial, published in The New England Journal of Medicine, demonstrated that once-weekly administration of semaglutide (2.4 mg), a long-acting GLP-1 receptor agonist, resulted in a mean body-weight reduction of 14.9 % over 68 weeks, with 86.4 % of participants achieving ≥5 % weight loss [10]. Subsequently, the SURMOUNT trials reported that the dual GIP/GLP-1 receptor agonist tirzepatide produced dose-dependent mean weight reductions ranging from approximately 15.0 % to 20.9 % over 72 weeks, with the greatest losses observed at the highest dose [9].

Despite the demonstrated benefits of semaglutide and tirzepatide, there is currently insufficient research analyzing the outcomes of pharmacological obesity treatment specifically in the geriatric population. The effects of these therapies on muscle preservation, nutritional status,

frailty, and the management of polypharmacy in older adults remain poorly understood. This paper aims to assess the clinical outcomes of GLP-1 and dual GLP-1/GIP agonists in elderly patients, addressing the current research gap regarding pharmacological obesity treatment in the geriatric population.

Aims of the study

The primary objective of this study is to provide a comprehensive evaluation of the clinical utility of glucagon-like peptide-1 (GLP-1) receptor agonists and dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) agonists in the management of obesity, with a particular focus on the geriatric population.

First, the research aims to assess the evidence regarding the efficacy and safety of these agents in adults with metabolic syndrome. Recent large-scale clinical trials have demonstrated that these therapies can achieve weight reductions exceeding 15–20% and lead to significant improvements in cardiometabolic markers, including blood pressure and lipid profiles [9,10]. Furthermore, the study evaluates the cardiovascular protective effects of these treatments, which have shown a 20% reduction in major adverse cardiovascular events (MACE) in overweight and obese populations without diabetes [11].

Second, this work seeks to identify the specific risks and potential benefits unique to geriatric patients, addressing the critical balance between weight loss and the preservation of lean body mass. Evidence suggests that while incretin-based therapies provide substantial metabolic advantages, they may also exacerbate the loss of muscle mass and bone mineral density. This poses a significant clinical challenge, potentially increasing the risk of sarcopenia and frailty syndrome in older adults [12, 13]. Moreover, the study analyzes the tolerance profile in the elderly, who may be more susceptible to gastrointestinal adverse events, leading to a higher risk of dehydration or malnutrition [13, 14].

Finally, the study intends to propose evidence-based clinical and research recommendations for this demographic. These include the necessity of integrating resistance exercise with pharmacotherapy to mitigate muscle loss and the implementation of personalized monitoring protocols, such as body composition analysis [12, 14]/. By synthesizing current data, this study aims to define the role of dual agonists in geriatric care and identify existing gaps in clinical evidence that require dedicated, geriatric-focused trials [13, 14].

Materials and methods

This systematic review was conducted through a comprehensive search of major electronic databases, including PubMed and Embase, and Scopus, for peer-reviewed studies published between 2020 and 2025. The methodology focused on identifying phase 2 and 3 randomized controlled trials as well as observational real-world evidence investigating the clinical application of GLP-1 receptor agonists and dual GLP-1/GIP agonists. The selection process was restricted to studies involving adults with obesity and metabolic syndrome, with a specific analytical focus on the geriatric population aged 65 years and older. Data were synthesized regarding primary efficacy endpoints, such as percentage weight loss and cardiovascular outcomes, alongside safety parameters including gastrointestinal tolerance and changes in body composition. The gathered evidence was qualitatively and quantitatively analyzed to identify trends in treatment outcomes and to address the specific clinical challenges associated with managing obesity in older patients, such as the risk of sarcopenia and frailty.

Results

Tirzepatide and semaglutide are highly effective medications used in the treatment of obesity. Tirzepatide is a dual agonist of the GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. It activates both GIP and GLP-1 receptors, which are natural incretin hormones in the human body. These receptors are located in brain areas involved in appetite regulation [9,15].

The SURMOUNT-1 trial evaluated the efficacy and safety of tirzepatide at doses of 5 mg, 10 mg, and 15 mg, combined with a low-calorie diet and increased physical activity, in adults without type 2 diabetes who had obesity or overweight. The results showed a clear dose-dependent effect on weight reduction. A weight loss of at least 20% was achieved by 16.5% of participants receiving 5 mg, 35.0% receiving 10 mg and 39.7% receiving 15 mg of tirzepatide, compared with only 0.3% in the placebo group [16].

Semaglutide is a synthetic agonist of the GLP-1 receptor. Its mechanism of action includes stimulation of GLP-1 receptors in the appetite-regulating centers of the central nervous system, which leads to reduced appetite and lower food intake [1].

The STEP (Semaglutide Treatment Effect in People with Obesity) program consists of several large, randomized phase 3 clinical trials that evaluated the effectiveness of semaglutide for

weight loss in adults with overweight or obesity. A review of STEP 1–4 showed that semaglutide at a dose of 2.4 mg was associated with an average weight loss of 14.9% to 17.4% compared with placebo in individuals without diabetes [17].

In patients treated only with semaglutide, a gradual weight loss of approximately 15–16% was observed after 12 months of treatment. In patients treated only with tirzepatide, weight loss ranged from 14–16%, although the number of patients in this group was smaller. Real-world data also indicate that only a proportion of patients reach the maximum recommended doses, which may limit the full therapeutic potential of these drugs [18,19].

In an open-label, controlled phase 3b trial comparing tirzepatide and semaglutide, adults with obesity were randomly assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or semaglutide (1.7 mg or 2.4 mg), administered once weekly by subcutaneous injection for 72 weeks [20].

Head-to-head comparative studies, including SURMOUNT-5, demonstrated that tirzepatide led to significantly greater weight reduction than semaglutide used at the standard anti-obesity dose. The average difference in total body weight loss was approximately 5–7 percentage points in favor of tirzepatide after about 72 weeks of treatment. Tirzepatide was also associated with a higher proportion of patients achieving clinically meaningful weight-loss thresholds (≥10%, ≥15%, and ≥20%) [9,18].

Overall, available studies indicate that tirzepatide shows greater weight-loss efficacy compared with semaglutide. In randomized controlled trials, mean weight reduction with tirzepatide ranged from 15% to 21%, depending on the dose (5–15 mg) and treatment duration. The greatest effects were observed with the 15 mg dose and long-term therapy [9].

Analyses of real-world clinical data confirm the high effectiveness of both medications, although the observed weight-loss effects are slightly smaller than those reported in randomized controlled trials. In a large retrospective cohort from an academic obesity clinic, the median weight loss was 9.4% after at least 6 months and 14.4% after at least 12 months of continuous treatment with GLP-1 receptor agonists [18].

Both randomized and observational studies show that weight reduction depends on the dose and duration of treatment. Higher doses of semaglutide (≥2 mg) and tirzepatide (≥10 mg) are associated with greater total weight loss, although differences in univariate analyses were

sometimes moderate. Multivariable models demonstrated that patients who reached higher doses within the first 9–12 months of treatment achieved significantly greater long-term weight reduction [18].

Overall, available evidence indicates that both semaglutide and tirzepatide are highly effective pharmacological options for the treatment of obesity. Tirzepatide consistently demonstrates greater weight-loss efficacy, while semaglutide remains an effective and widely used therapeutic option. Real-world clinical data confirm the effectiveness of both drugs and highlight the importance of long-term treatment, appropriate dose titration, and sustained adherence [19,21].

Currently, direct large randomized controlled trials comparing tirzepatide and semaglutide specifically in older adults (e.g., ≥65 years, with dedicated subgroup analyses) are very limited. Most available RCTs include the general adult population with overweight or obesity rather than a geriatric population. However, post hoc analyses of the SURPASS-1 to SURPASS-5 trials evaluated the effects of tirzepatide in participants aged ≥65 years with type 2 diabetes and a BMI <30 kg/m², indicating the absence of obesity [22].

These analyses showed that older adults treated with tirzepatide experienced significant weight loss and a meaningful reduction in HbA1c compared with baseline values. Weight reduction in this group was dose-dependent but slightly smaller than in the overall SURPASS population. Treatment discontinuation due to adverse events was more frequent among older participants, although the overall incidence of adverse events remained low. Importantly, no increased risk of hypoglycemia was observed in older patients treated with tirzepatide, even when used in combination with insulin or sulfonylureas [22].

The safety profile of both medications is mainly characterized by gastrointestinal adverse events. In clinical trials, 6.1% of participants receiving tirzepatide discontinued treatment due to adverse events, compared with 8.0% of participants receiving semaglutide. Reported adverse events included gastrointestinal symptoms, renal impairment, gallbladder disease, pancreatitis, and hypoglycemia [2,18,23]. Overall, treatment discontinuation due to adverse events occurred in a small percentage of patients and was more common at higher doses [23].

Discussion

The available evidence indicates that glucagon-like peptide-1 (GLP-1) receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 (GIP/GLP-1) receptor agonists exhibit substantial therapeutic potential in the management of obesity and metabolic syndrome, including in older adults. Randomized clinical trials and real-world data consistently demonstrate marked efficacy with respect to body weight reduction and improvement in key metabolic parameters such as glycemic control, lipid profile, and blood pressure. Weight loss in the range of 15-20%, particularly observed with tirzepatide, may translate into clinically meaningful reductions in cardiovascular risk, which is of particular relevance in older populations characterized by a high burden of cardiometabolic comorbidities. Nevertheless, in geriatric patients, these benefits must be carefully balanced against age-specific risks associated with intentional weight loss.

In older adults, weight reduction does not necessarily reflect a selective loss of adipose tissue and may be accompanied by a disproportionate decline in fat-free mass, including skeletal muscle. This phenomenon may accelerate the development of sarcopenia, frailty, functional impairment, and increased risk of falls, potentially offsetting the metabolic advantages of pharmacological treatment. Moreover, gastrointestinal adverse effects commonly associated with incretin-based therapies, such as nausea, vomiting, and diarrhea, may have more pronounced clinical consequences in elderly individuals, predisposing them to dehydration, malnutrition, and exacerbation of chronic conditions. Available analyses also suggest a slightly higher rate of treatment discontinuation among older participants, underscoring the importance of careful patient selection and close clinical supervision.

From a practical perspective, the use of GLP-1 and GIP/GLP-1 receptor agonists in older patients requires a highly individualized approach. Beyond routine monitoring of body weight, systematic assessment of nutritional status, body composition, and muscle function is essential. Gradual dose titration may improve treatment tolerability and reduce the incidence of adverse events. Furthermore, effective management should involve close interdisciplinary collaboration, including geriatricians, dietitians, and rehabilitation specialists, to ensure adequate protein intake and implementation of resistance exercise programs aimed at preserving muscle mass and functional capacity. Particular caution is warranted in patients with polypharmacy and impaired renal function, in whom the risk of complications may be increased.

Despite the promising findings reported to date, the current evidence base remains limited by the lack of large, prospective randomized controlled trials specifically designed for geriatric

populations. Future studies should include predefined age strata, such as individuals aged ≥65 or ≥75 years, and incorporate outcomes that are highly relevant to older adults, including muscle strength, incidence of falls, hospitalization rates, functional status, and quality of life. In addition, longer follow-up periods after treatment discontinuation are needed to evaluate the durability of therapeutic effects and the clinical implications of potential weight regain. High-quality real-world data should complement randomized trials to better characterize safety and effectiveness in routine clinical practice, particularly among the oldest and most medically complex patients.

In conclusion, GLP-1 receptor agonists and dual GIP/GLP-1 agonists represent a promising therapeutic option for the treatment of obesity in older adults. However, their use should be approached with caution and guided by individualized risk-benefit assessment. Careful patient selection, comprehensive monitoring, and integration of pharmacotherapy with nutritional and exercise interventions are essential. Dedicated geriatric-focused clinical trials are urgently needed to define the optimal role of these agents in the comprehensive management of obesity and metabolic syndrome in the aging population.

Conclusion

The evidence gathered in this study confirms that incretin-based therapies—particularly tirzepatide and semaglutide—are game-changers in obesity management, with tirzepatide showing a distinct advantage in total weight reduction. However, applying these results to geriatric care is not straightforward. Our findings suggest a "double-edged sword" effect: the profound weight loss (often exceeding 15–20%) carries a significant risk of accelerating muscle depletion and frailty in older adults. Moving forward, the clinical priority must shift from simple weight reduction to "quality of weight loss." This means that pharmacological intervention in the elderly should never be a standalone treatment; it must be coupled with structured resistance training and aggressive nutritional support to safeguard muscle mass. Ultimately, the current lack of dedicated trials for the 65+ age group represents a major gap in our knowledge. Future research needs to look beyond the scale and focus on functional outcomes like grip strength, fall risk, and overall quality of life to truly define the safety of these drugs in an aging population.

Author's contribution

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