



Review Article

GLP-1 Based Therapies for Obesity in Older Adults: Current Evidence and Emerging Treatments

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Submitted : 13 August, 2026

Accepted : 03 September, 2026

Published : 04 September, 2026

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Abstract

Obesity is rising in prevalence among older adults (individuals over the age of 65 years) and is associated with cardiometabolic conditions, sarcopenia, frailty, and mobility limitations. This age group is particularly susceptible to the loss of lean mass and physical function, even though intentional weight loss may improve metabolic and functional health. This highlights the need for personalized treatment. GLP-1-based therapies affect appetite, energy intake, body weight, and cardiometabolic risk, making them key pharmacological therapies for managing obesity. This review addresses the available evidence on oral semaglutide, semaglutide, tirzepatide, and liraglutide, as well as the novel oral agent orforglipron for obesity management in older adults. While multiple clinical trials in general adult populations have reported clinically meaningful weight loss and improvements in cardiometabolic outcomes, evidence specifically derived from adults aged ≥65 years remains underrepresented, and data for those aged ≥75 years are particularly scarce. Important factors to consider in older adults include sarcopenic obesity, preservation of lean mass, polypharmacy, and gastrointestinal adverse effects. Oral preparations may provide additional treatment options for individuals who have concerns about injectable administration. Future research should prioritize older adults and assess functional outcomes, body composition, and effects on sarcopenia.

Introduction

Obesity has become one of the defining public health challenges of the 21st century; the prevalence of this condition is growing steadily. More than one billion people worldwide are currently estimated to be living with obesity, and projections indicate this number will continue climbing through 2030. This burden is especially evident in older adults, as the prevalence of obesity in this age group increased by about 20% in recent years [1]. In addition to the musculoskeletal, cardiometabolic, and mental health comorbidities associated with obesity at any age, older adults face an elevated risk of sarcopenia. While weight loss is generally associated with improvements in comorbidities, quality of life, and healthcare costs in younger adults, this benefit cannot be assumed in older adults, given concerns that weight loss may exacerbate sarcopenia and reduce bone density [2].

Given the difficulty of achieving durable lifestyle change in older populations, anti-obesity medications have emerged as a valuable pharmacological complement to the evidence-based approaches to obesity treatment. Among the pharmacological treatments available, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become the first choice for obesity management, owing to their well-documented effects on controlling appetite and on energy intake through both central and peripheral mechanisms [3]. The launch of new oral forms of GLP-1 RAs has also broadened the range of treatment options, offering a needle-free alternative that may improve accessibility and adherence in older populations. This review examines the current evidence on GLP-1-based therapies, including new oral formulations, for the treatment of obesity in older adults, with particular emphasis on their cardiometabolic benefits and their clinical significance for sarcopenia.

For this review, older adults are defined as individuals aged ≥ 65 years. Evidence specifically derived from adults aged ≥ 75 years is discussed separately when available, as this population may have greater frailty, sarcopenia, and functional vulnerability. Studies that define older populations using a lower age threshold, such as ≥ 60 years, are identified separately and should not be interpreted as directly equivalent to evidence specifically obtained in adults aged ≥ 65 years.

Obesity and sarcopenia in older adults

In older adults, obesity is an increasingly prevalent condition, and it embodies a major public health concern. In the United States, nearly 42% of older adults live with obesity, with prevalence continuing to rise [4]. Older adults with obesity are more likely to develop osteoarthritis, frailty, mobility limitations, and cardiometabolic diseases, as well as other age-related conditions [5-6]. As people age, body composition undergoes significant changes, including reduced muscle mass and increased total and visceral adiposity [5,7]. These changes occur even though body weight remains the same. This is explained by a decline in lean mass, which is counteracted by an increase in fat mass [5,8]. Age-related decline in physical activity, hormonal changes, anabolic resistance, and metabolic alterations further contribute to these variations in composition of older adults [7,8].

Sarcopenic obesity refers to a high-risk condition that is defined by the presence of sarcopenia and obesity, incorporating excess adiposity with concurrently age-related reductions in muscle mass, physical function, or strength. In older adults, SO is a condition that results from metabolic, inflammatory, and hormonal factors and is predictive of an increased risk of functional decline and other adverse health outcomes [7].

Weight loss in older adults requires particular attention to body composition, even though intentional weight loss can improve physical function and metabolic health. This concomitant loss of fat and lean tissue can be a result of caloric restriction and pharmacologically induced weight loss [9,10]. This is of particular concern in individuals who already have low functional reserve, sarcopenia, or frailty. Current proposed approaches reinforce that resistance exercise and protein intake help preserve muscle mass [10].

Use of Glp-1-Based therapies in older adults

Tirzepatide

In November 2023, the U.S. Food and Drug Administration (FDA) approved tirzepatide for chronic weight management in adults with obesity (BMI ≥ 30 kg/m²) or overweight (BMI ≥ 27 kg/m²) with at least one weight-related comorbidity, in combination with a reduced-calorie diet and increased physical activity. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that activates both incretin pathways. Through GIP and GLP-1 receptor activation, tirzepatide enhances glucose-dependent insulin secretion and reduces appetite and food intake, while GIP receptor activation may provide additional metabolic effects that complement GLP-1 receptor signaling [11].

The efficacy of tirzepatide for obesity treatment was demonstrated in the SURMOUNT-1 trial, in which adults with obesity or overweight without diabetes achieved substantial, dose-dependent weight loss over 72 weeks, with mean reductions of up to 20.9% at the 15-mg dose; moreover, more than half of participants receiving the 10- and 15-mg doses achieved at least 20% weight loss [12]. These findings demonstrate substantial efficacy in the general adult population; however, SURMOUNT-1 was not specifically designed to evaluate adults aged ≥ 65 years or ≥ 75 years.

These findings were further supported by the SURMOUNT-4 trial, which examined the durability of weight loss after an initial 36 weeks of tirzepatide therapy. Participants who continued tirzepatide achieved additional weight loss during the following 52 weeks, whereas those who switched to placebo experienced substantial weight regain. These findings indicate that continued tirzepatide treatment is important for maintaining the weight-loss benefits achieved with therapy [13].

Tirzepatide has also demonstrated cardiovascular and functional benefits in adults with obesity and heart failure with preserved ejection fraction (HFpEF). In the SUMMIT trial, which enrolled 731 adults aged ≥ 40 years with a mean age of 65.2 years, tirzepatide reduced the risk of the composite outcome of cardiovascular death or worsening heart failure compared with placebo, with the benefit primarily driven by a reduction in worsening heart-failure events. Treatment also improved health status, quality of life, and functional capacity. Although the mean age of the study population was within the older-adult range, SUMMIT was not specifically designed to evaluate outcomes in adults aged ≥ 65 or ≥ 75 years. Therefore, these findings should be interpreted as evidence from a general adult population with substantial representation of older adults, rather than as direct evidence of efficacy specifically in adults aged ≥ 65 years or ≥ 75 years [14].

Liraglutide

Liraglutide is a GLP-1 RA; its primary mechanisms—including appetite reduction, delayed gastric emptying, and enhanced insulin action—are particularly important in older adults who exhibit increased visceral fat and impaired metabolism due to sarcopenia and low-grade inflammation. It is recommended for long-term weight management in adult patients with an initial body mass index (BMI) of ≥ 30 kg/mm² or ≥ 27 kg/m² in the presence of at least one weight-related comorbid condition (hypertension, T2DM, or dyslipidemia) [15].

Evidence specifically addressing older adults remains more limited than evidence from the general adult population. In a retrospective cohort study of 32 adults aged ≥ 60 years with obesity, Oral et al. evaluated the effect of liraglutide 3.0 mg on body weight over 24 weeks. Participants had a mean age of 63.8 years, a mean baseline weight of 94.31 ± 14.82 kg, and a mean BMI of 36.49 ± 5.34 kg/m². Liraglutide was associated with progressive weight loss, with mean reductions of 5.96% at 4 weeks, 10.06% at 8 weeks, 13.85% at 12 weeks, and 15.80%

at 24 weeks (all $P < .0001$). At week 24, all participants achieved at least 5% and 10% weight loss from baseline. Nausea was the most frequently reported adverse effect. These findings suggest that liraglutide may provide substantial weight reduction in older adults with obesity; however, the interpretation is limited by the small sample size, the inclusion of participants aged ≥ 60 years rather than exclusively ≥ 65 years, and concomitant lifestyle intervention [16].

Age-specific analyses of the SCALE Obesity and Prediabetes and SCALE Diabetes trials provide additional evidence in adults aged ≥ 65 years. In the SCALE Obesity and Prediabetes trial, participants aged ≥ 65 years treated with liraglutide 3.0 mg had a mean weight reduction of 8.4%, compared with 4.2% with placebo. In the SCALE Diabetes trial, mean weight reduction among participants aged ≥ 65 years was 7.2% with liraglutide 3.0 mg compared with 2.5% with placebo. There was no significant interaction between treatment and age group, suggesting that the efficacy of liraglutide 3.0 mg was broadly comparable between adults aged ≥ 65 years and younger adults. However, older adults represented a relatively small proportion of the study populations, and data in adults aged ≥ 75 years were limited. Gastrointestinal adverse events were more frequent with liraglutide, and the proportion of participants reporting adverse and serious adverse events tended to increase with age [1].

Liraglutide has also demonstrated cardiovascular benefits in older adults with T2DM at high cardiovascular risk. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, liraglutide reduced the risk of major adverse cardiovascular events (MACE) compared with placebo, with a greater relative reduction observed among participants aged ≥ 75 years, in whom the risk of MACE was reduced by 34%. Liraglutide was also associated with reductions in all-cause mortality, with a 6% relative risk reduction among participants aged 60–74 years and a 35% reduction among those aged ≥ 75 years [17].

Semaglutide

Semaglutide is a long-acting GLP-1 RA that enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and acts on central appetite-regulating pathways to reduce hunger and caloric intake, resulting in improved glycemic control and substantial weight loss. Semaglutide 2.4mg once weekly was approved for chronic weight management in adults with overweight and at least one weight-related comorbidity or obesity in 2021. The efficacy of semaglutide 2.4 mg once weekly was demonstrated in the Semaglutide Treatment Effect in People with Obesity (STEP) program trials across a range of populations, with achievement of placebo-subtracted weight loss of 12%–15% in individuals without type 2 diabetes [18]. However, it should be noted that the STEP trials enrolled general adult populations rather than being specifically designed to evaluate efficacy in older adults. Consequently, while these trials provide strong evidence supporting semaglutide's efficacy in adults with overweight or obesity, generalizing these findings to adults aged ≥ 65 years—and particularly to those aged ≥ 75 years—should be undertaken with caution.

In the STEP 1 trial, participants without type 2 diabetes lost an average of 14.9% of their body weight on semaglutide 2.4mg, compared with 2.4% on placebo, alongside gains in physical functioning and improvements in cardiometabolic markers such as BMI, waist circumference, and blood pressure [19]. STEP 2 produced comparable results in participants who had both obesity and type 2 diabetes, with 9.6% weight loss versus 3.4% on placebo [20]. The contribution of central satiety pathways to this weight loss was reinforced in STEP 3, where adding behavioral therapy pushed the reduction to 16% with semaglutide compared with 5.7% with placebo [21]. STEP 4 made clear that continuing treatment is essential to sustain these effects — stopping the drug led to substantial weight rebound [22]. Long-term durability was confirmed in STEP 5, where participants held onto an average weight loss of 15.2% over 104 weeks, compared with 2.6% in the placebo group [23]. Collectively, these trials establish the efficacy and durability of semaglutide for weight management in the general adult population. However, because these studies were not specifically designed to evaluate adults aged ≥ 65 or ≥ 75 years, the available findings should not be interpreted as direct evidence of efficacy in these age groups.

Cardiovascular benefits are also well established for semaglutide. SUSTAIN 6 and PIONEER-6 trials evaluated adults with type 2 diabetes at elevated cardiovascular risk and demonstrated cardiovascular benefits with semaglutide [24]. In addition, the SELECT trial demonstrated a 20% reduction in major adverse cardiovascular events (MACE) among adults with overweight or obesity and established cardiovascular disease but without diabetes [25]. Although these findings are clinically relevant to older adults, the cardiovascular trials were conducted in general adult populations rather than exclusively in adults aged ≥ 65 or ≥ 75 years. Therefore, cardiovascular evidence for semaglutide should be distinguished from evidence derived specifically from age-defined older populations.

Injectable semaglutide has confirmed efficacy and safety for the treatment of obesity, but utilization remains very low, fewer than 2%. Oral medication provides a new option for treating obesity and may provide an alternative for individuals who are afraid of injections and may simplify storage they usually does not require a refrigerated supply chain. Oral semaglutide is absorbed in the stomach and is formulated with the absorption enhancer, an N-acetylated salicylic acid-derived amino acid (SNAC), that enables effective gastric absorption. This makes it the first FDA-approved peptide drug formulated with SNAC [3,26].

The OASIS clinical trial evaluated the safety of using 50 mg once daily vs. placebo for weight management in adults without T2DM. The dose is significantly higher than the subcutaneous dose due to a difference in bioavailability. In OASIS 1, oral semaglutide 50 mg demonstrated greater weight loss than placebo over the course of 68 weeks. The newly approved formulations of 25 mg and 50 mg (Wegovy) differ from 14 mg (Rybelsus) in providing greater weight reduction. However, little data is available regarding oral semaglutide in older adults, and further research is needed to determine its impact on functional outcomes in this population [26].

The PIONEER trial showed that treatment with oral semaglutide 14 mg was associated with significant weight loss of 2.3 kg, while 0.5 mg and 1 mg of subcutaneous semaglutide were associated with 3.73 and 4.53 kg reduction, respectively. However, this trend is also seen when comparing SUSTAIN 8 and PIONEER, but they are not compared with a statistical test using the original patient-level data. Therefore, we should not make conclusions about the superiority of administering one over the other [27,28].

The PIONEER trial showed a higher rate of treatment discontinuation due to AEs with increasing age. Around 9% in individuals aged over 65 years compared to 7% under 65 years [29–30]. The AEs are similar to those with injectable treatment, including GI symptoms, occurrence of acute pancreatitis, gallbladder disease, suicidal ideation, medullary carcinoma, acute kidney injury, and worsening of diabetic retinopathy [28].

Orforglipron

Orforglipron is a synthetic, orally bioavailable, small-molecule, nonpeptide GLP-1 RA. In the United States, Orforglipron was approved on 01 April for the management of obesity or in adults with overweight who have one or more weight-related comorbid conditions. It was originally designed to overcome the intrinsic limitations, especially poor oral bioavailability and rapid enzymatic degradation. It can be taken at any time during the day and must be taken daily [31,32]. The recommended starting dose is 0.8 mg, with dose escalation up to 17.2 mg based on response and tolerability [32].

The Phase 2 trials enrolled adults 18–75 years of age and showed dose-dependent weight loss. In addition, there was demonstrated improvement in glycemic levels and a reduction in appetite in 7–10% at 26 weeks. The ATTAIn trials showed a decrease in weight of 12–15%. In addition, these trials showed meaningful metabolic improvement (reduced waist circumference, improvement in body composition, and metabolic biomarkers) and cardiovascular risk reduction. Some obesity trials demonstrated a reduction in systolic blood pressure, triglycerides, LDL cholesterol, and inflammatory markers, as well as an increase in HDL cholesterol. Phase 1–3 trials did not show a significant change in serum creatinine, estimated glomerular filtration rate, or urinary albumin excretion. As seen in the ACHIEVE-1 and ATTAIn studies, renal function remained stable. GI AEs were also associated; they are usually self-limited, and hypoglycemia remains uncommon. There was no association with pancreatitis, retinal detachment, or ischemic optic neuropathy [31,32]. As with other GLP-1 RAs, it has a concerning risk of thyroid C-cell tumor seen in rats and mice [32].

It is important to mention that older adults were underrepresented in the original clinical trials. There is a recent post-hoc analysis of ATTAIn-1 and 2 that evaluates participants aged over 65 years, including 616 participants of the 4740, showing a weight reduction of 7.9%, 11.3%, and 13% in treatment with orforglipron 5.5, 9, and 17.2 mg, respectively, at 72 weeks, compared with 1.6% with placebo. Therefore,

these results were comparable to those observed in younger participants, suggesting that the efficacy is maintained in older adults [33]. The evidence for older adults remains limited, especially since the available studies did not further stratify outcomes for adults aged ≥ 75 years. In addition, it is important to keep in mind that outcomes related to bone density, nutritional status, muscle mass, and physical function were not evaluated [31,32].

The available evidence for GLP-1-based therapies in older adults varies considerably by agent, particularly with respect to representation of adults aged ≥ 65 years and ≥ 75 years. A summary of the mechanisms, routes of administration, major clinical trials, efficacy, adverse effects, and limitations of the available evidence is presented in Table 1.

Special considerations in older adults

An estimate of 11% of older adults live with sarcopenic obesity (SO), with no significant variation by sex [6]. SO encompasses the overlap of obesity and reduced lean muscle mass and function; being heavily linked to disability, mortality, and reduced quality of life [7]. This condition is facilitated by aging, hormonal changes, chronic inflammation, and chronic diseases [6,7,34]. Protein supplementation, exercise, calorie restriction, and smoking remain important strategies to prevent SO [7–9].

In adults aged 65 years and older, GLP-1-based therapy appears to favor reductions in adipose tissue, although its effects on lean mass may vary. In older adults with obesity and diabetes, semaglutide preserves skeletal muscle percentage while still reducing body weight, BMI, fat mass, and skeletal muscle mass [35]. Consistent findings were observed in two older women, in whom tirzepatide produced substantial lean mass loss with modest fat mass loss, whereas semaglutide produced a modest gain in lean mass with substantial fat mass loss [36].

Polypharmacy is described as the standard use of five or more medications, and affects nearly one in three older adults, increasing with age. It is commonly associated with drug interactions, non-adherence, falls, mortality, cognitive decline, and hospitalization [37,38]. It is essential to acknowledge that GLP-1 RAs may alter the absorption of co-administered medications, making a reconciliation necessary [39].

Gastrointestinal adverse effects, particularly nausea, vomiting, diarrhea, and constipation, are typically mild and influenced by dosage and the concomitant use of medications [40–42]. GLP-1 RAs are contraindicated in medullary thyroid carcinoma or MEN 2, as thyroid C-cell tumor remains a concern [39, 42–43]. Importantly, in older adults with CKD, GLP-1 RAs require cautious use due to a higher rate of gallbladder events and renal adverse effects [40, 44–46].

Patient-centered treatment and quality of life

In older adults with obesity, the treatment should be individualized depending on the patient's overall health status, functional capacity, comorbidities, frailty, and nutritional

Table 1: Summary of GLP-1-based therapies for obesity in older adults.

Therapy	Mechanism / Route	Major trials	≥65 / ≥75 years evidence	Efficacy	Limitations
Tirzepatide	GIP/GLP-1 RA; SC weekly	SURMOUNT-1, -4; SUMMIT	SUMMIT mean age 65.2 yr; ≥75 limited [14]	Up to 20.9% [12]	Limited ≥65/≥75- specific evidence; GI AEs
Liraglutide	GLP-1 RA; SC daily	SCALE; LEADER	≥65: efficacy demonstrated; ≥75 limited [1,17]	8.4% vs 4.2%; 7.2% vs 2.5% [1]	Small older-adult representation; GI AEs
Semaglutide	GLP-1 RA; SC weekly	STEP 1–5; SUSTAIN-6; PIONEER-6; SELECT	≥65: limited; ≥75: very limited	14.9% vs 2.4%; 15.2% vs 2.6% [19,23]	Limited age-specific evidence; weight regain after withdrawal
Oral Semaglutide	GLP-1 RA + SNAC; oral daily	OASIS; PIONEER	≥65: limited; ≥75: limited [29-30]	OASIS: substantial; PIONEER: ~2.3 kg [26-28]	Limited ≥75/functional data; GI AEs
Orforglipron	Oral nonpeptide GLP-1 RA; oral daily	ACHIEVE; ATTAIN	≥65/≥75: limited data [31-33]	~12–15% [31-32]	Limited long-term/oldest-old data; GI AEs

Abbreviations: AE, adverse event; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SC, subcutaneous; SNAC, sodium N-[8-(2-hydroxybenzoyl)amino]caprylate.

status. GLP-RAs can accomplish clinically meaningful weight loss, but it should not be the sole purpose. It is important to keep in mind that preservation of muscle mass, physical function, and quality of life may be equally or more important outcomes. Therefore, the use of GLP-1 RAs requires a patient-focused approach, and treatment goals should be established through shared decision-making [47,48].

It is important when choosing which GLP-1 RAs to use to take into consideration the patient's preferences, as they may influence treatment adherence and acceptance. Some older adults may prefer oral medication due to concern about injections or self-administration issues, while others may prefer injectable administration to avoid adding another daily medication [28–32,39,48]. In addition, it is important to take into consideration gastrointestinal tolerability, polypharmacy, cost, medication administration, and insurance coverage [39, 48].

Finally, the goal of obesity treatment in older adults should be focused on achieving clinically significant benefits without compromising nutrition status, lean muscle, or independence. To ensure these benefits, regular follow-up visits and reassessments of body weight, hydration status, muscle mass, functional capacity, and tolerability should be conducted to provide appropriate control [1,47].

Conclusion

GLP-1-based therapies are key therapies for older adults with obesity. The different trials have demonstrated a safe and effective therapeutic option with semaglutide, liraglutide, and tirzepatide. However, there are still not enough studies available on the impact of oral medication in older adults. The use of GLP-1-based therapies in older adults requires finding a balance between achieving significant weight loss and preserving muscle mass, physical functionality, and quality of life.

In addition, special focus is needed on the physiological changes associated with aging, such as sarcopenia, frailty, nutritional vulnerability, and polypharmacy. Since new therapies continue to arise, it is vital for future research to focus on identifying which treatment would benefit older adults, determining the most appropriate route of administration, and evaluating outcomes that extend beyond the number on the

scale. A more patient-centered evidence base will be essential to have a better picture of the safety and effectiveness of these therapies in the long-term management of obesity in older adults.

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