Treating Sarcopenic Obesity in the Era of Incretin Therapies: Perspectives and Challenges

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Sarcopenic obesity, a subtype of obesity, is marked by reduced skeletal muscle mass and function, or sarcopenia, and poses a significant health challenge to older adults as it affects an estimated 28.3% of people aged >60 years. This subtype is unique to older adults as aging exacerbates sarcopenia and obesity due to changes in energy metabolism, hormones and inflammatory markers, and lifestyle factors. Traditional treatments for sarcopenic obesity have been focused on exercise and dietary modifications to reduce fat while maintaining muscle mass. Newer glucagon-like peptide 1 receptor agonists (GLP-1RA) and dual gastric inhibitory polypeptide/GLP-1 receptor agonists (GIP/GLP-1RAs), including liraglutide, semaglutide, and tirzepatide, have shown great promise to reduce weight, treat obesity-related complications, improve physical function, and improve quality of life, in younger clinical trial populations. However, the use of GLP-1RAs and GIP/GLP-1RAs has not been exhaustively evaluated in older adults with sarcopenic obesity. These medications come with the risk of loss of muscle mass and an increased rate of adverse events. Thus, clinicians should use them cautiously by weighing the potential benefits against their risks. Herein, we discuss a possible approach to using GLP-1RAs and GIP/GLP-1RAs in patients with sarcopenic obesity, including considerations for patient identification, monitoring, maintenance, and discontinuation. In this article we also discuss the emerging treatments that will be available, which may include activin type II receptor antibodies and selective androgen receptor agonists. We conclude by highlighting the advancement of geroscience as a promising field for individualizing treatments in the future.

ARTICLE HIGHLIGHTS

- Sarcopenic obesity, reduced muscle mass and strength coupled with obesity, poses significant health risks to older adults.
- Aging exacerbates sarcopenia and obesity due to metabolic, hormonal, inflammatory, and lifestyle changes.
- Traditional interventions emphasize exercise and diet to reduce fat mass while preserving muscle mass.
- Incretin therapies show promise in weight reduction and physical improvement in younger populations but are minimally studied in older adults.
- These medications can be used to treat several obesity-related complications, which older adults with sarcopenic obesity are prone to developing.
- These medications need to be used cautiously among older adults, considering potential muscle mass loss and adverse events.

Obesity, defined as a BMI of $\geq$30 kg/m^2, is a highly prevalent chronic disease among older adults, affecting more than 40% of this population (1). Many older adults have lived with obesity for an extended period, increasing their risk of developing complications, including diabetes, cardiovascular disease, and osteoarthritis (2). Sarcopenia, as defined by the Global Leadership Initiative in Sarcopenia consortium, is a disease of skeletal muscle dysfunction defined as a reduction in both muscle mass and strength, and results in significant morbidity and mortality (3). Sarcopenic

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obesity, recently defined by the Sarcopenic Obesity Global Leadership Initiative consensus, is a subtype of obesity characterized by the existence of both obesity and sarcopenia (4). The presence of the two diseases leads to a synergistically higher combined risk of metabolic impairments and functional decline than with either alone (5). Its estimated prevalence ranges from 4.4% to 84.0% for men and from 3.6% to 94.0% for women, depending on the definition used (6), although most recent estimates indicate that 28.3% of people aged >60 years are affected by this syndrome (7). The treatment of sarcopenic obesity remains complex, as many weight loss therapies result in the loss of both fat and muscle mass (8). In this article, we discuss the pathophysiology of sarcopenic obesity, review traditional therapies, and explore how practitioners can use glucagon-like peptide 1 receptor agonists (GLP-1RAs) and dual gastric inhibitory polypeptide/GLP-1 receptor agonists (GIP/GLP-1RAs) in treating this at-risk population.

PATHOPHYSIOLOGY OF SARCOPENIC OBESITY

Both the prevalence of sarcopenia and the prevalence of obesity increase with increasing age, and their co-occurrence synergistically accelerates the progression of both conditions (5). This synergy is the result of many factors, which include aging-related changes in energy metabolism and body composition, hormonal and inflammatory pathways, and dietary and lifestyle factors (5) (Fig. 1). Throughout the aging process, multiple factors result in an increase in fat mass and a reduction in muscle mass. Well-established epidemiological studies indicate that body fat increases until the seventh decade of life (9), while muscle mass begins to decline after the fourth decade of life (10). Thus, at this time, most weight that is gained is fat, in part due to a decline in resting metabolic rate and total energy expenditure, without a commensurate reduction in drive to eat (11,12).

Increased fat mass thereby activates an inflammatory cascade that results in muscle loss and intramyocellular lipid deposition (5) (Fig. 2). Adipose cells activate immune cells (e.g., mast cells, T cells, macrophages), upregulating leptin and inhibiting adiponectin, which in turn increases proinflammatory cytokines interleukin-6 and tumor necrosis factor-α (5). A proinflammatory state results throughout both the body and within muscle, resulting in intramyocellular lipid deposition, lipotoxicity, and inhibition of both muscle contractility and muscle protein synthesis (5). Some of these changes are additionally mediated and amplified by hormonal pathways as a result of aging (13), leading to decreased levels of anabolic hormones that then drive muscle synthesis and affect signals such as insulin-like growth factor, estrogen, and testosterone (13), while catabolic hormones, such as cortisol, are increased (14).

Lifestyle factors also contribute to the development of sarcopenic obesity. Exercise has positive effects on muscle structure and function, but older adults are also prone to physical inactivity (15). Muscle contractions caused by exercise result in nitric oxide release in the muscle (16), which improves insulin sensitivity (17) and promotes enhanced muscle protein synthesis (18). Exercise induces reductions in myostatin and increases in IGF-I levels and improves the anabolic effects of insulin in the muscle, further promoting muscle synthesis (19). Muscle function is also improved through aerobic and resistance exercises through nutrient-stimulated vasodilation, improved nutrient delivery to muscle, and enhanced mitochondrial function (20). Thus, a lack of exercise initiates a vicious cycle where muscle mass and strength may be reduced and physical function is impaired, leading to inactivity, leading to further reductions in fat-free mass and gains in fat mass (21). Dietary intake is also a contributing factor to the development of sarcopenic obesity. Due to an obesogenic environment, dietary quality lacking in adequate nutrients

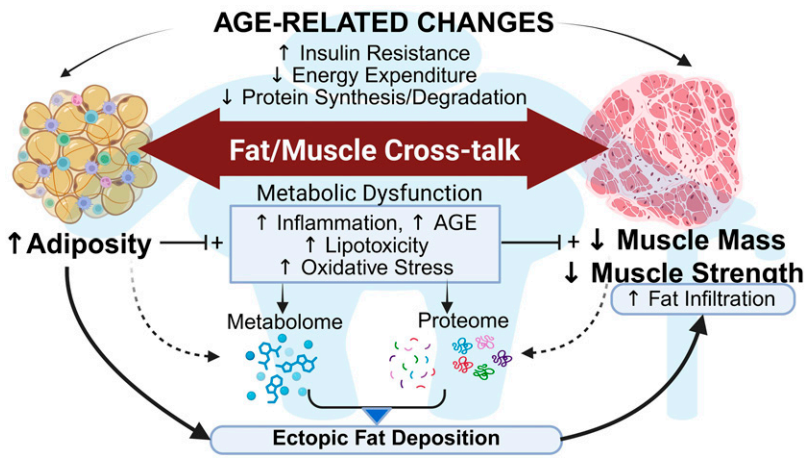

Figure 1—Overview of mechanisms leading to sarcopenic obesity. Complex interactions between adipose cells and myocytes result in a reduction in muscle mass and muscle strength due to multiple mechanisms. AGE, advanced glycemic end product.

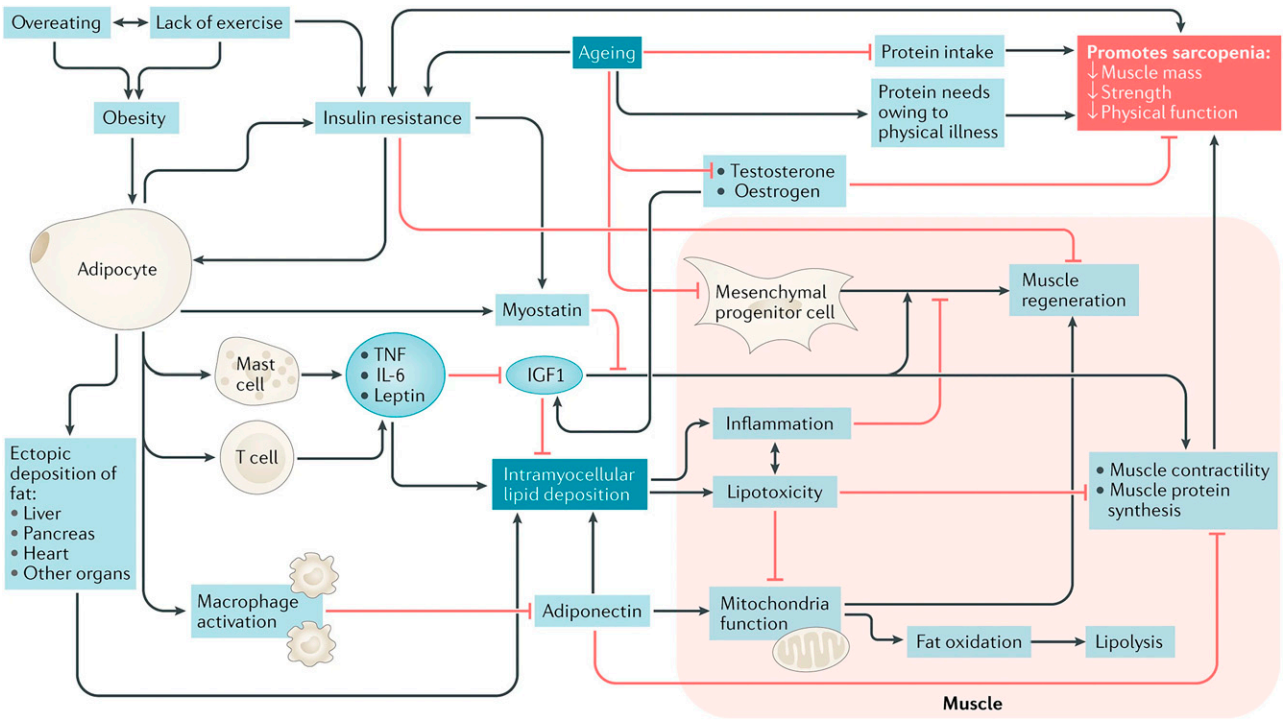

Figure 2—A proposed model of cellular mechanisms leading to sarcopenic obesity. Black lines indicate stimulatory interactions, and red lines with flat ends indicate inhibition. IL, interleukin; TNF, tumor necrosis factor. Adapted from Batsis and Villareal (5).

results in increased adiposity and reduction in muscle mass (8,22). Older adults may be less likely to take in adequate amounts of protein or micronutrients, including vitamin D, thereby both precipitating increases in fat mass and potentially leading to sarcopenia (23).

HISTORY OF WEIGHT REDUCTION TREATMENTS FOR SARCOPENIC OBESITY

Treatment of sarcopenic obesity has traditionally been centered on dietary modifications and exercise interventions aimed at reducing fat mass while preserving muscle mass, with the goal of improving physical function. In several meta-analyses investigators have examined the effect of dietary and exercise interventions on adults with sarcopenic obesity (24–26) . Resistance exercise has been shown to improve gait speed, lower-extremity strength, and physical function testing (25,26). However, exercise did not consistently reduce weight, reduce body fat, or increase fat-free mass (24,26). Studies in these meta-analyses are limited by low quality of evidence, heterogeneity in interventions, variable definitions used for sarcopenic obesity, and short follow-up times (most were 8–36 weeks). Thus, the evidence for exercise therapies is often extrapolated from older adults with obesity, where data show that exercise can improve physical function and maintain muscle mass (27,28). Resistance training is recommended for patients with sarcopenia alone to improve muscle mass, strength, and physical function (29).

To our knowledge, there are no well-designed trials adequately powered to test specific dietary modifications for sarcopenic obesity where newer definitions for sarcopenic obesity are used (5). Calorie restriction in older adults has been shown to result in loss of both fat mass and fat-free mass (30), and whether the rate of muscle mass loss differs in patients with sarcopenic obesity is unknown. Systematic reviews and meta-analyses of dietary interventions for sarcopenic obesity show that nutritional interventions decrease fat mass but do not consistently improve fat-free mass (24,26). Protein supplementation in people with sarcopenic obesity has not been shown to improve body fat percentage or fat mass (24), although protein supplementation is recommended for adults with sarcopenia alone with weak evidence rating (29). Again, studies in these meta-analyses are limited by low quality of evidence, heterogeneity of interventions, variable definitions of sarcopenic obesity, and short follow-up time (24,26). A systematic review of 20 clinical trials, with older adults enrolled and testing of dietary energy restriction interventions with high protein intake (≥1.0 g/kg/day), showed that high protein intake resulted in a higher percentage of retained fat-free mass and more fat mass loss in comparison with normal protein intake (31).

In a high-quality randomized controlled trial (RCT) with 93 older adults with obesity, where participants were randomized to a diet group (500–750 kcal energy deficit with 1 g high-quality protein/kg body wt/day), exercise group (both resistance and aerobic), or diet-exercise group,

important insights were provided on the impact of diet and exercise on weight and body composition (30). After 12 months, physical function measured with the physical performance test increased most in the diet-exercise group (mean 5.4 ± SD 2.4 points), compared with the exercise group (4.0 ± 2.5 points), diet group (3.4 ± 2.4 points), and control group (0.2 ± 1.8 points). Weight reduction was similar between the diet-exercise (8.6 ± 3.8 kg) and the diet (9.7 ± 5.4 kg) groups but less in the exercise group (1.8 ± 2.7 kg). Fat-free mass decreased more in the in the diet-exercise group (1.8 ± 1.7 kg) than the diet group (3.2 ± 0.2 kg). Fat-free mass increased by 1.3 ± 1.6 kg in the exercise group. Fat mass decreased by 6.3 ± 2.8 kg in the diet-exercise group, 7.1 ± 3.9 kg in the diet group, and 1.8 ± 1.9 kg in the exercise group. While these results provide promise for the addition of exercise to dietary interventions to preserve fat-free mass, adherence limits the effectiveness of exercise and dietary modifications (32).

Bariatric surgery is a highly effective means of weight reduction in patients with obesity, but it has been minimally studied in older adults, with even fewer studies in individuals with sarcopenic obesity (8). In a systematic review and meta-analysis of 34 trials, investigators evaluated the body composition changes after bariatric surgery (33). They found that while the loss in fat mass was substantial (weighted mean difference 25.7 kg [95% CI 20.1–34.8]), patients lost 9.7 kg (95% CI 10.8–8.7) of fat-free mass. This loss was greatest with biliopancreatic diversion (11.5 kg [95% CI 5.2–17.8]), followed by Roux-en-Y gastric bypass (10.0 kg [9.0–11.0]), sleeve gastrectomy (9.5 kg [7.1–11.9]), and gastric banding (7.0 kg [4.4–9.5]). However, mean ages for the studies included ranged from 16 to 56 years; therefore, fat-free mass loss may differ among older adults. In one observational study of 69 patients undergoing bariatric surgery, investigators found that there was no difference in weight reduction between patients with and patients without sarcopenic obesity (28.6% vs. 27.4%, respectively) after 12 months (34). Fat-free mass (measured with bioelectrical impedance) was similar between sarcopenic and nonsarcopenic groups 12 months after surgery (mean 29.2 ± SD 2.0 vs. 30.5 ± 1.0 kg). However, these results may have less external validity for older adults, as the mean age (years) was in the mid-40s, an outdated definition of sarcopenic obesity was used in the study, and bioelectrical impedance was used for evaluation of fat-free mass, with which there are variable results depending on method used and level of hydration (35). Thus, additional data are needed for understanding of the use of bariatric surgery in older adults with sarcopenic obesity.

EXPLORING USE OF GLP-1RAS AND GIP/GLP-1RAS IN OLDER ADULTS WITH SARCOPENIC OBESITY BASED ON AVAILABLE EVIDENCE

Newer medications for treatment of obesity, including GLP-1RAs and GIP/GLP-1RAs, have changed the landscape of obesity treatment. These medications, including liraglutide, semaglutide, and tirzepatide, can result in significant and sustained weight reduction (averaging up to 15%–25% body weight) (36–38). To our knowledge, there are no data available specifically addressing use of GLP-1RAs and GIP/GLP-1RAs for treatment of older adults with sarcopenic obesity. Despite this gap, we summarize trials where use of GLP-1RAs and GIP/GLP-1RAs has been evaluated in other populations to explore possible benefits and harms of these treatments for older adults with sarcopenic obesity.

An important caveat in all trials to date is that <1 in 10 participants in large obesity treatment clinical trials for GLP-1RAs or GIP/GLP-1RAs were older adults, leaving a research gap in how older adults respond to these medications (36–38). In a systematic review of RCTs, investigators found that only four studies included analysis of a subgroup of older adults (age ≥65 years): two studies of liraglutide, one of semaglutide, and one of tirzepatide (39). The largest analysis of older adults taking a GLP-1RA or GIP/GLP-1RA is a secondary analysis of Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) (n = 6,728), a cardiovascular outcomes trial of semaglutide for people with BMI ≥27 kg/m^2, which showed an estimated treatment difference (ETD) from −7.5% to −8.1% body weight change over 59 months (40). In a subgroup analysis of 20 older adults in SURMOUNT-1, a clinical trial testing the weight reduction effect of tirzepatide, an ETD of −18.2% was found between the tirzepatide group and placebo group (41). While not exclusively limited to older adults, two trials tested semaglutide in adults with heart failure, with more older adults enrolled than in prior weight reduction trials (median age 69 years for both trials). In the Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction (STEP-HFpEF) trial and the Semaglutide Treatment Effect in People with Obesity and Heart Failure with Preserved Ejection Fraction and Diabetes Mellitus (STEP-HFpEF DM) trial, adults with obesity and heart failure with preserved ejection fraction were randomized to either semaglutide or placebo for 52 weeks (42,43). In STEP-HFpEF, adults with type 2 diabetes were excluded, and STEP-HFpEF DM included adults with type 2 diabetes. The ETD in body weight change between semaglutide and placebo was −10.7% (95% CI −11.9 to −9.4) in STEP-HFpEF and −6.4% (−7.6 to −5.2) in STEP-HFpEF DM. Overall, these results show that older adults lose substantial weight with either GLP-1RAs or GIP/GLP-1RAs, but data are lacking and whether older adults with sarcopenic obesity were enrolled is unknown.

Clinical trials with testing of the weight reduction effect of GLP-1RAs and GIP/GLP-1RAs have shown both improved subjective physical function but also loss of fat-free mass, often used as a surrogate for muscle mass in analyses with DXA (36–38,44). Trials to test subjective physical function included use of the physical functioning

score on the health status questionnaire 36-Item Short Form Health Survey (SF-36) (scores ranging from 19.0 to 57.6). In Semaglutide Treatment Effect in People with Obesity (STEP 1) (mean age 46 years), a large clinical trial for testing the weight reduction effect of semaglutide with comprehensive lifestyle interventions, ETD between semaglutide and placebo groups was 1.8 points (95% CI 1.2–2.4), favoring semaglutide (38). In a subgroup analysis of participants who had poor physical function at baseline, the gains in physical function for the semaglutide group were even greater, with an ETD of 5.6 points (95% CI 3.6–7.7) (45). Within a subgroup whose body composition was measured with DXA (mean age 46 years), participants taking semaglutide lost 3.6% of their fat-free mass, vs. 0.1% in the placebo group (38). In SURMOUNT-1 (mean age 44.9 years), participants taking tirzepatide had more improvement in subjective physical function in comparison with participants taking placebo (4.2 [95% CI 3.7–4.7] vs. 1.9 [1.4–2.4], respectively) (36). Within the DXA substudy of SURMOUNT-1 (mean age 46 years), participants treated with tirzepatide lost 10.9% of their fat-free mass compared with 2.6% in the placebo group (36). Participants in the Satiety and Clinical Adipose Liraglutide Evidence (SCALE) Obesity and Prediabetes trial (mean age 45 years), an RCT with testing of the weight reduction effect of liraglutide, also had reductions in physical function (mean change not stated in the article) (37). RCTs have also shown liraglutide, semaglutide, and tirzepatide to improve quality of life, measured with the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) questionnaire, for measuring quality of life in three domains (physical function, physical, and psychosocial) (36–38,46). An analysis combining results from STEP 1–2 showed that participants taking semaglutide had more improvement in all of the domains of the IWQOL-Lite-CT, with total score ETD of 10 points (95% CI 8.4–77.6) in STEP 1 and 3.6 points (1.2–5.9) in STEP 2 between semaglutide and placebo (45). A combined analysis of STEP 1–4 showed that patients taking semaglutide also had improvement in almost all domains of the SF-36, which includes physical function, pain, social functioning, and mental health (45). These data are from younger populations who likely did not have preexisting sarcopenic obesity. Thus, it is unclear whether the fat-free mass loss will be different in older adults with sarcopenic obesity and whether they will still have improvements in physical function and quality of life when their amount of muscle mass and function is at a lower level.

GLP-1RAs and GIP/GLP-1RAs have been shown to provide benefit for many obesity-related complications. The SELECT trial enrolled adults age ≥45 years with BMI ≥27 kg/m^2 and preexisting cardiovascular disease (47). A total of 17,604 participants (mean age 61.6 years) were enrolled in the trial, and findings showed lower incidence (6.5%) among participants treated with semaglutide of the primary outcome (composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) in comparison with the placebo group (8.0%). Semaglutide was also tested in a trial with adults with obesity and heart failure with preserved ejection fraction in STEP-HFpEF and STEP-HFpEF DM (42,43), as mentioned above. Participants in both trials (STEP-HFpEF, n = 529 and median age 69 years, and STEP-HFpEF DM, n = 616 and median age 69 years) randomized to semaglutide reported improvement in heart failure symptoms and physical limitations (measured with the Kansas City Cardiomyopathy Questionnaire clinical summary score [KCCQ-CSS], range 0–100) in comparison with the placebo group. In STEP-HFpEF the ETD was 7.8 (95% CI 4.8–10.9) and in STEP-HFpEF DM the ETD was 7.3 (4.2–10.4), showing that participants taking semaglutide had improvements in their KCCQ-CSS. Tirzepatide was tested in two RCTs in Japan with adults with moderate-to-severe obstructive sleep apnea and obesity (BMI ≥30 and ≥27 kg/m^2). One trial included adults who were not receiving positive airway pressure (n = 234, mean age 47.9 years), and the other trial included adults who were receiving positive airway pressure (n = 235, mean age 51.7 years) (48). In both trials, treatment with tirzepatide resulted in a greater reduction in the apnea hypopnea index, a measure of severity of sleep apnea, in comparison with placebo. For adults in the nonpositive airway pressure trial, the ETD showed a decrease in the apnea hypopnea index by 20 events/h (14.2–25.8). For adults in the positive airway pressure trial, the ETD showed a decrease in apnea hypopnea index by 23.8 events/h (17.9–29.6). Semaglutide was tested in an RCT with adults with obesity and moderate-to-severe pain due to osteoarthritis (n = 407; mean age 56 years) (49). After 68 weeks of treatment, adults taking semaglutide had an improvement in Western Ontario and McMaster Universities Osteoarthritis Index (scaled 0–100 with higher scores reflecting worse outcomes) in comparison with the placebo group (ETD −14.9 points [95% CI −20.4 to −9.3]). Therefore, there is mounting evidence that GLP-1RA and GIP/GLP-1RA medications improve obesity-related complications. While the prevalence of these conditions in older adults with sarcopenic obesity has not been described, these complications develop in part as a result of the proinflammatory adipokines and insulin resistance that are present in adults with sarcopenic obesity (50). Therefore, the treatment of obesity-related complications is important in this group.

Despite these potential benefits, the adverse events of these GLP-1RAs and GIP/GLP-1RAs have been minimally studied in older adults, given their limited enrollment in large RCTs. A systematic review identified only two RCTs of liraglutide that reported adverse events specifically in older adults. Described in a single abstract, these RCTs indicated an increase in adverse events with age, especially gastrointestinal side effects. In an analysis of

Japan-based trials testing semaglutide for treatment of type 2 diabetes, rate of adverse events among older adults was similar to that among younger adults, but the trial was discontinued due to side effects at a higher rate (51).

GLP-1RAs and GIP/GLP-1RAs can induce weight reduction in older adults; however, the magnitude of free fat mass loss in older adults with sarcopenic obesity is unknown. Depending on the amount of muscle mass loss, it is possible that older adults with sarcopenic obesity will have improvements in physical function as younger populations have (36–38). Benefits in treatment of obesity-related complications, like cardiovascular disease and sleep apnea, could be particularly valuable to older adults with sarcopenic obesity (47–49). Despite these potential benefits, the side effect profile of GLP-1RAs and GIP/GLP-1RAs in older adults is problematic, with higher discontinuation rates (39,51), although the rates among people with sarcopenic obesity remain virtually unknown, highlighting the potential for benefits and yet unknown harms (Fig. 3).

RECOMMENDATIONS FOR USING GLP-RAS OR GIP/GLP-1RA IN PATIENTS WITH SARCOPENIC OBESITY

While additional studies are performed to clarify the benefit of treating patients with sarcopenic obesity with GLP-1RAs and GIP/GLP-1RAs, clinicians should approach their use with caution in the population. Clinicians must weigh the potential benefit in terms of physical function and obesity-related complications with harms such as gastrointestinal symptoms, polypharmacy, and reduction in muscle mass (Table 1 and Fig. 4).

On initiation of GLP-1RA or GIP/GLP-1RA treatment for patients, a thorough evaluation of their physical function is crucial. Patients with obesity can be screened for sarcopenic obesity with use of criteria developed by the Sarcopenic Obesity Global Leadership Initiative (52) (Fig. 5). Older adults with obesity can be screened for surrogate parameters for sarcopenia, which include clinical symptoms or risk factors like chronic diseases or age >70 years. If clinicians suspect sarcopenia, a two-step evaluation of muscle mass and function is needed. Altered skeletal muscle function can be evaluated using hand dynamometers or a Timed Up & Go test. Muscle mass can be estimated using DXA or bioelectrical impedance. The presence of both altered skeletal muscle function and reduction in skeletal muscle mass relative to body weight is sufficient for diagnosing sarcopenic obesity. Further details on the diagnosis of sarcopenic obesity can be found in the consensus guideline (52).

While it is critical that GLP-1RA and GIP/GLP-1RA therapy does not worsen the physical function of older adults with sarcopenic obesity, which patients may be prone to worse functional outcomes, based on preexisting functional impairment and sarcopenia, is unknown. Patients suitable for GLP-1RA or GIP/GLP-1RA therapy should be able to adhere to resistance training recommendations and adequate intake of dietary protein (see below) to prevent excess loss of fat-free mass (44). It may be beneficial to trial patients regarding these recommendations prior to starting GLP-1RA or GIP/GLP-1RA therapy to ensure they can adhere to them. Furthermore, it is essential to rule out any contraindications, such as chronic pancreatitis or gastroparesis or other contraindications, that could render GLP-1RAs or GIP/GLP-1RAs unsafe (53–55). Medication lists should be evaluated for any other medications that might compete with or counteract the effects of GLP-1RA or GIP/GLP-1RA therapy.

While there is no clear preferred GLP-1RA or GIP/GLP-1RA for patients with sarcopenic obesity, there are some important considerations. First, treatment of concurrent obesity-related complications should be considered. Semaglutide can be used in patients with heart failure symptoms, preexisting cardiovascular disease, and pain from osteoarthritis (42,47,49). Tirzepatide can be used in patients with obstructive sleep apnea (48). There are trials ongoing with testing of tirzepatide

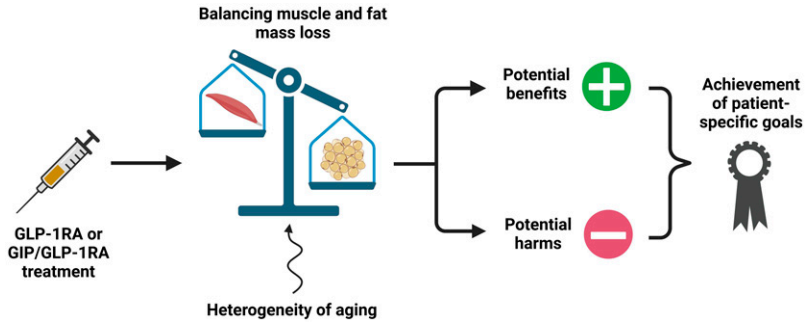

Figure 3—Conceptual model of the balance of muscle and fat loss in treatment of sarcopenic obesity in older adults. Treatments for sarcopenic obesity should be focused on balancing the reduction in fat mass with concomitant reduction in muscle mass. This balance will be impacted by patient-specific factors that are heterogeneous within the population of older adults, such as pretreatment body composition, chronic diseases, genetic factors, and lifestyle factors. The effect of treatment on the balance of fat and muscle loss will result in benefits (e.g., treatment of obesity-related complications, improvement in physical function and quality of life) and harms (e.g., muscle and bone mass loss, adverse events, polypharmacy). Ideally, the net effect of these benefits and harms will achieve patient-specific goals.

Table 1—Recommended approach to treating older adults with sarcopenic obesity with GLP-1RAs and GIP/GLP-1RAs

Phase of treatment	Considerations	Evidence
Patient selection/initiation	All patients should be evaluated for impairments in physical function. We recommend that patients considered appropriate for GLP-1RAs or GIP/GLP-1RAs not have severe physical function impairments,* not have contraindications (such as chronic pancreatitis, gastroparesis), and not be taking any competing medications.	Guidance for diagnosing sarcopenic obesity (4). Contraindications listed on drug label (53–55)
Treatment choice	Consider choosing a GLP-1RA or GIP/GLP-1RA with less rapid weight reduction or increasing the dose of the GLP-1RA or GIP/GLP-1RA at a slower rate than recommended on drug packaging. Obesity-related complications should be targeted with treatment. Treatment should be coupled with exercise and dietary modifications.	Mean body weight reduction with GLP-1RAs and GIP/GLP-1RAs (57). Effects of different GLP-1RAs and GIP/GLP-1RAs on obesity-related complications (42,47–49). Resistance exercise and protein supplementation maintain free fat mass (44). Patients taking antiobesity medications may need supplementation of micronutrients (63). Patients taking liraglutide lost more fat mass and maintained more fat-free mass if they exercised (61)
Monitoring	Monitor patients every 1–3 months during ramp-up phase.* Monitor for adverse events including dehydration, weakness, falls. Adjust other medications as necessary. Follow body composition if able.	Gastrointestinal side effects should be expected to last 2–8 days, and constipation may last past 40 days (64). GLP-1RAs and GIP/GLP-1RAs reduce fat-free mass (38)
Maintenance	The lowest effective dose should be maintained.* Effect should be defined according to health goals, such as physical function, benefits for other chronic diseases (e.g., treatment of diabetes, reduction in blood pressure), and quality of life, as opposed to solely weight reduction.*	Authors' expert opinion
Discontinuation	Any severe adverse event, worsening of muscle weakness, or loss of physical function should prompt medication discontinuation.	U.S. Food and Drug Administration drug labels (53–55)

GIP, gastric inhibitory polypeptide. *Based on authors' expert opinion.

and semaglutide in other obesity-related diseases. Observational studies of GLP-1RAs have shown cognitive benefits, with clinical studies underway (56). Thus, these indications will change as new data emerge. Second, the amount or rate of weight reduction should be considered. A network meta-analysis of clinical trials of antiobesity medications showed weight reduction to be 4.7% for liraglutide, 11.4% for semaglutide, and 12.4% for tirzepatide—notable lower than in earlier trials of GLP-1RAs and GIP/GLP-1RAs (57). Clinicians should consider which agent may be most appropriate for the amount of weight reduction needed for their patient or the amount that can be tolerated, keeping in mind that muscle mass loss will occur with any weight reduction (44,58). In studies comparing gradual weight reduction and rapid weight reduction using dietary interventions, gradual weight reduction resulted in more fat mass loss with equal fat-free mass loss (59). Further, rapid weight reduction with a very-low-calorie diet is associated with the formation of gallstones (60), and other side effects may be more prevalent with rapid weight reduction. Thus, the dose escalation described on medication packaging may be too fast for older adults with sarcopenic obesity. Dose escalation should be closely titrated based on side effects and weight reduction velocity.

In addition to treatment with GLP-1RAs or GIP/GLP-1RAs, patients should be counseled on exercise and nutritional interventions to maintain skeletal muscle mass and physical function. Resistance exercise can improve muscle mass and function in patients with sarcopenic obesity (8). A trial with randomization of patients to liraglutide, exercise, or exercise plus liraglutide showed that patients in the exercise plus liraglutide group lost more fat mass than the other two groups and maintained more fat-free mass than the liraglutide group (61). The American College of Sports Medicine advises that adults engage in a strength training regimen at least twice a week on nonconsecutive days (62). For healthy adults, this should include one set of 8–12 repetitions, while older or more frail individuals should aim for one set of 10–15 repetitions. It is recommended that resistance training include both slow- and fast-velocity movements, with initial focus on one or two sets of 8–12 repetitions at ∼65% of the individual's one-repetition maximum. Over time, the aim should be to increase to two or three sets at 75% of one-repetition maximum. As

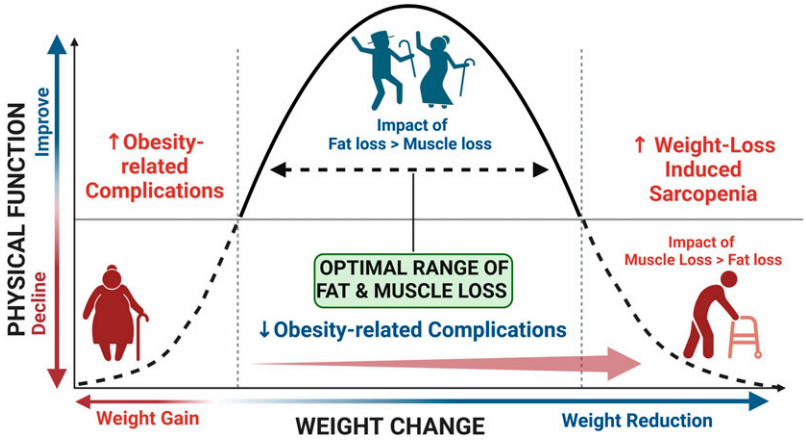

Figure 4—Continuum of weight change and its relationship with physical function in older adults with sarcopenic obesity. Across the continuum of weight change, there are variable effects on physical function. With weight gain and substantial weight reduction, there may be worsened physical function. There is likely an optimal range of fat and muscle mass loss that improves the physical function of older adults with sarcopenic obesity, while treating obesity-related complications.

reduction of caloric intake has been shown in patients taking GLP-1RAs or GIP/GLP-1RAs, it is important that the nutritional intake of older adults taking GLP-1RAs or GIP/GLP-1RAs be monitored to ensure they are intaking adequate macro- and micronutrients (63). Protein intake of 1.0–1.2 g/kg body wt (or 1.2–1.5 g/kg body wt for patients with multimorbidity) is recommended to increase and maintain muscle mass and physical function (8,29). Monitoring of micronutrient intake, especially of vitamin D, calcium, and Ω-3 fatty acids, which are important to muscle health, is also recommended, with supplementation if needed (8,63).

Close and regular monitoring is essential, especially during the initial dose-escalation phase of GLP-1RA or GIP/GLP-1RA therapy. Patients with sarcopenic obesity should ideally be seen either in person or virtually every 1 to 3 months, allowing for timely detection and management of any severe adverse effects such as dehydration, weakness, or falls. Gastrointestinal side effects (nausea, diarrhea, vomiting, constipation) are common with these medications. Pooled analyses of three semaglutide RCTs showed that nausea, vomiting, and diarrhea lasted 2–8 days (64). However, the median duration of constipation was 47 days, and thus older adults should be proactively monitored with care managed for this symptom. Slowing the dose-escalation phase may reduce the incidence of gastrointestinal side effects (65). In addition to monitoring for these adverse events, it is also necessary to adjust other medications as required to avoid any potentially harmful drug interactions. Tracking body composition, if feasible, can provide valuable insights into the patient's response to therapy and help guide any necessary adjustments to the treatment plan. This may be limited due to availability of equipment or insurance coverage for testing. Physical function should be monitored with an inventory of activities of daily living and strength testing. The Timed Up & Go test can easily be done in an office setting or during a virtual encounter to monitor physical function (64).

More research is needed for understanding of the relationship between medication dose and changes in body composition and function; thus, the optimal dose of GLP-1RA or GIP/GLP-1RA that should be recommended for older adults with sarcopenic obesity is unknown. The primary outcome measure should not solely be weight reduction; rather, achievement of broader health goals should also be included. These goals can comprise improved physical function, benefits for other chronic conditions such as better diabetes management and reduced blood pressure, and overall enhancement of quality of life (Fig. 3).

GLP-1RA or GIP/GLP-1RA therapy should be discontinued immediately if the patient experiences any severe adverse events (53–55). A notable worsening of muscle weakness or a significant loss of physical function represented by new impairments in activities of daily living, worse scores on strength or functional testing, or falls are strong indicators that the therapy may no longer be suitable or safe for the patient. Anecdotally, in our clinical practice, we have observed older adults (predominantly age >85 years) whose rapid weight loss has led to functional decline, weakness, frailty, and falls. Prompt discontinuation under such circumstances is crucial to prevent further harm. Notably, weight regain will occur with cessation of therapy. While it is unknown whether weight regained will be of the same composition as weight lost, there is speculation that weight regain may be less if patients engage in resistance exercise with GLP-1RA or GIP/GLP-1RA therapy (66). As more agents are tested and discovered, patients with sarcopenic obesity may be able to switch to more suitable options.

FUTURE OF THE TREATMENT OF SARCOPENIC OBESITY IN THE ERA OF HIGHLY EFFECTIVE ANTIOBESITY MEDICATIONS

GLP-1RAs and GIP/GLP-1RAs appear to be just the tip of the iceberg of new therapies for the treatment of obesity

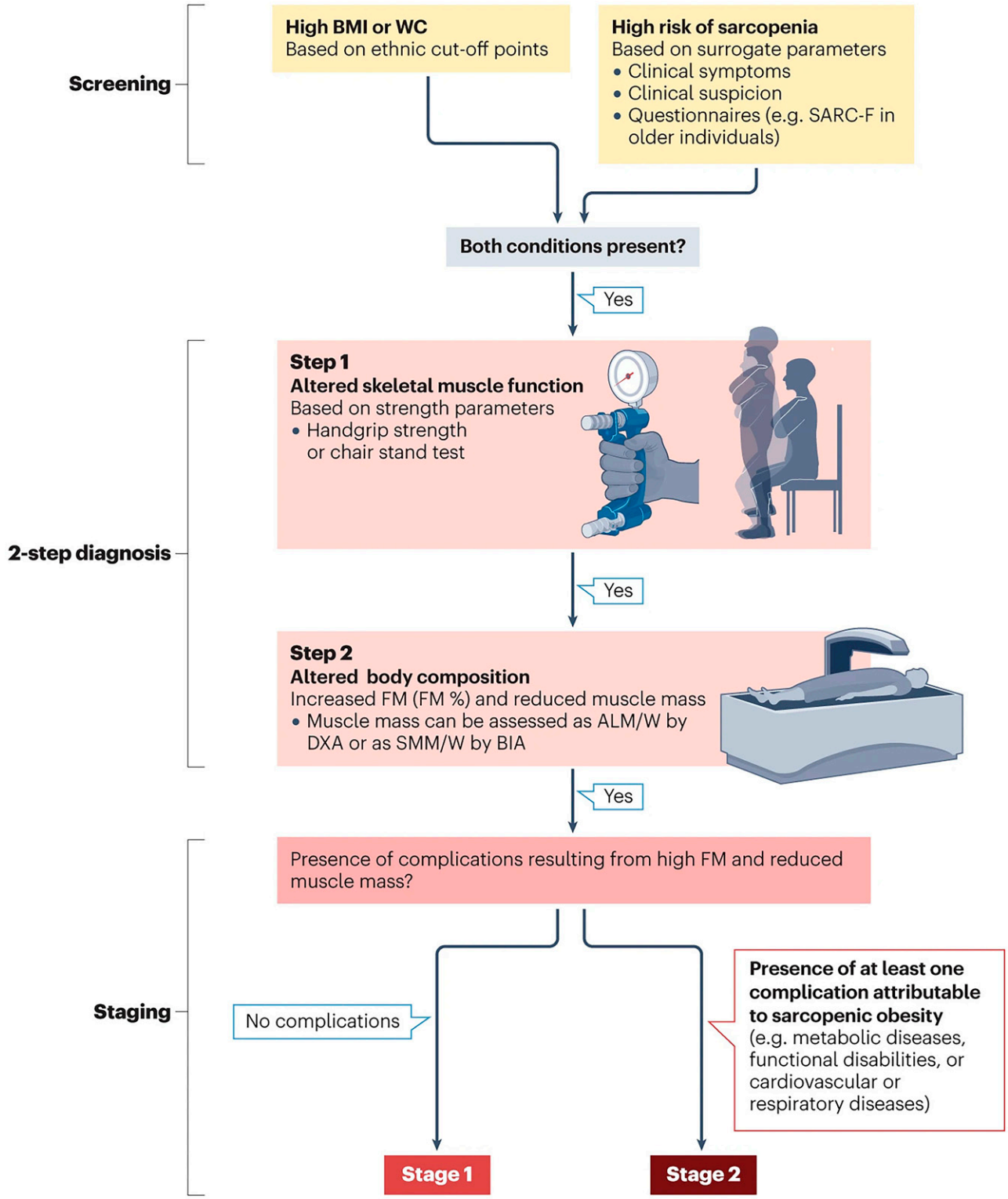

Figure 5— Proposed algorithm for screening and diagnosis of sarcopenic obesity. This algorithm is based on the consensus statement from the Sarcopenic Obesity Global Leadership Initiative group (52). ALM/W, appendicular fat-free mass/weight; BIA, bioelectrical impedance analysis; FM, fat mass; SARC-F, Strength, Assistance in walking, Rise from a chair, Climbing stairs, and Falls (questionnaire); SMM/W, skeletal muscle mass/weight; WC, waist circumference. Adapted from Prado et al. (8).

(67). There are many other medications in development that activate nutrient-stimulated hormones like glucagon-like peptide 1 and gastric inhibitory polypeptide and may have better side effect profiles, with less muscle mass loss (67). Sarcopenia-specific pharmacotherapies are also being developed that may benefit patients with sarcopenic

obesity (68). Clinical trials are underway to test the effect of activin type II receptor antibodies, like bimagrumab, trevogrumab, and garetosmab, in patients with sarcopenia. Multiple early studies have shown selective androgen receptor modulators, which demonstrate androgenic activity in muscle, to increase fat-free mass and physical function (5,68,69). The company developing enobosarm, a selective androgen receptor modulator, recently reported preliminary results of a phase 2b RCT showing that in patients receiving semaglutide for weight reduction, those who also took enobosarm had 71% less loss of fat-free mass in comparison with those only receiving semaglutide (70). Additional research is needed for understanding of the long-term effects of these medications, their effect on physical function, their impact on obesity-related complications like cardiovascular disease, and their side effect profile.

Aging is a highly heterogeneous process, influenced by a combination of genetic, environmental, and lifestyle factors, making the treatment of sarcopenic obesity in older adults complex. This variability necessitates a nuanced understanding of the aging process and the biology of sarcopenic obesity. The advancement of geroscience, a field that integrates biology, genetics, and physiology with the goal of developing treatments to slow aging and delay age-related diseases, provides promise for new therapies for sarcopenic obesity (71). Multiple pathways overlap with some of the metabolic mechanisms that precipitate sarcopenic obesity; thus, future therapies to prolong healthy aging may also treat sarcopenic obesity. Future work could focus on integrating clinical factors, biomarkers, and patient goals into decision aids to support treatment decisions regarding the initiation of current and emerging therapies for patients with sarcopenic obesity.

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Author Contributions. A.S.C. conceptualized the manuscript; researched the literature; drafted, reviewed, and edited the manuscript; and approved the final version of the manuscript. J.A.B. conceptualized the manuscript; provided key resources; drafted, reviewed, and edited the manuscript; and approved the final version of the manuscript. A.S.C. and J.A.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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