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Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies

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Abstract

Weight loss induced by glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual glucagon-like peptide-1 receptor (GLP-1R)/glucose-dependent insulinotropic polypeptide receptor agonists is coming closer to the magnitudes achieved with surgery. However, with greater weight loss there is concern about potential side effects on muscle quantity (mass), health and function. There is heterogeneity in the reported effects of GLP-1-based therapies on lean mass changes in clinical trials: in some studies, reductions in lean mass range between 40% and 60% as a proportion of total weight lost, while other studies show lean mass reductions of approximately 15% or less of total weight lost. There are several potential reasons underlying this heterogeneity, including population, drug-specific/molecular, and comorbidity effects. Furthermore, changes in lean mass may not always reflect changes in muscle mass as the former measure includes not only muscle but also organs, bone, fluids, and water in fat tissue. Based on contemporary evidence with the addition of magnetic resonance imaging-based studies, skeletal muscle changes with GLP-1RA treatments appear to be adaptive: reductions in muscle volume seem to be commensurate with what is expected given ageing, disease status, and weight loss achieved, and the improvement in insulin sensitivity and muscle fat infiltration likely contributes to an adaptive process with improved muscle quality, lowering the probability for loss in strength and function. Nevertheless, factors such as older age and severity of disease may influence the selection of appropriate candidates for these therapies due to risk of

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sarcopenia. To further improve muscle health during weight loss, several pharmacological treatments to maintain or improve muscle mass designed in combination with GLP-1-based therapies are under development. Future research on GLP-1-based and other therapies designed for weight loss should focus on more accurate and meaningful assessments of muscle mass, composition, as well as function, mobility or strength, to better define their impact on muscle health for the substantial number of patients who will likely be taking these medications well into the future.

KEYWORDS

cardiovascular disease, GLP-1 receptor agonist, insulin resistance, muscle, obesity, sarcopenia, type 2 diabetes

1 | INTRODUCTION

Recent studies have shown that pharmacologically assisted weight loss with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual glucagon-like peptide-1 receptor (GLP-1R)/glucose-dependent insulinotropic polypeptide receptor agonists (GIP-RAs) is approaching magnitudes close to that achieved with bariatric surgery.[1,39,92] However, with greater weight loss there is concern about potential adverse effects on muscle quantity (mass), health and function, especially in more vulnerable patients. Lean body mass, although contentious, is widely used as a surrogate measurement for muscle mass.[3] Lean body mass is calculated as the difference between total body weight and body fat weight, or more simply, the weight of all body tissues and fluids except the fat. The range of lean body mass considered to be healthy is approximately 70%–90%, with women being towards the lower end of the range and men in the higher end of the range. Maintenance of lean mass is important during weight loss because muscles and internal organs have a higher metabolic rate than the equivalent weight of fat. Consequently, maintenance of lean body mass facilitates a higher metabolic rate and makes it easier to lose and maintain body weight during a weight loss intervention. Describing the impact and clinical significance of reductions in lean mass, and especially muscle mass, with GLP-1-based weight loss is important to understand the quality of the weight loss achieved. One important question is whether the loss of muscle mass associated with weight loss treatments is adaptive (i.e., a physiological response to weight loss maintaining or minimally affecting muscle health/function), or maladaptive (i.e., adversely impacting muscle health/function). The aim of this review was to provide the most contemporary evidence addressing changes in lean body mass and muscle composition with GLP-1-based therapies and potential mitigation strategies in current use and in development. Focus was placed on the complex interplay between muscle quantity, composition and function, and metabolic physiology and the impact of GLP-1-based treatments, as well as on the challenges and opportunities associated with methods of assessing and addressing muscle health and sarcopenia during weight loss.

2 | MUSCLE PHYSIOLOGY IN OBESITY AND WEIGHT LOSS

There is an established association between body weight and muscle mass. Persons living with obesity commonly have more muscle mass than those with normal weight, and weight loss (from any intervention) is associated with loss of muscle mass. Weight loss from diet, pharmacotherapy, surgery or disease typically reaches a plateau.[4] In addition, a significant portion of the weight lost is usually regained after 1 year, and most patients regain most of the weight lost after 5 years.[5] A major reason for this observation is the homeostatic control of body weight, leading to reduced energy expenditure with weight loss. To a large extent, the reduction in muscle mass contributes to this adaptation, as each kilogram of muscle mass lost reduces resting energy expenditure by approximately 13 kcal/day. This is in contrast to the amount contributed by each kilogram of fat mass (~4 kcal/day).[4] Weight loss also reduces the mass of other organs such as the liver, heart and kidneys, for which the basal metabolic rate is several times higher than that of skeletal muscle. This physiology is complex, however, as some tissues are more energetically active and utilize more energy than others, and loss of some organ weight (e.g., fat from the liver) may actually improve metabolism. In a weight loss trial (low-calorie diet) following women with overweight and obesity, changes in total tissue mass during weight loss accounted for 60% of the reduction in basal metabolic rate, while the remaining 40% was due to increased energy efficiency (known as metabolic adaptation or adaptive thermogenesis).[6] If muscle mass could be maintained or even increased during weight loss, it could limit the reduction in metabolic rate and concomitant homeostatic adaptation, leading to a slowing or plateau in weight loss.

Skeletal muscle attributes are described by both quantity (size and number of myocytes, i.e., hypertrophy vs. hyperplasia) and quality (composition), which are influenced by obesity. For example, compared to persons with normal weight, those living with obesity have more muscle mass but greater relative weakness, as well as reduced mobility and function. This could partly be explained by obesity being associated with lower muscle quality (myosteatosis and muscle fibre composition), as evidenced by decreased muscle strength (slower maximal shortening velocity and lower specific force and normalized

power of the muscle fibres),[7] which could contribute to functional and metabolic abnormalities. Skeletal muscle is the main tissue responsible for insulin-stimulated glucose disposal and an impaired uptake is common in obesity and has substantial impact on whole-body glucose turnover.[8,9] Studies indicate that weight gain and loss correlate with decreasing and increasing insulin sensitivity, respectively.[10] It has been shown that moderate lifestyle-induced weight loss of 5% is associated with loss of lean mass but improvement in skeletal muscle, adipose tissue and liver insulin sensitivity, indicating less quantity but improved quality.[11,12] Short-term calorie restriction (~30% calorie reduction) decreases the postprandial rate of muscle protein synthesis and maintains or decreases basal muscle protein synthesis.[11,12] However, prolonged reduction of caloric intake, leading to the common target of 5%–10% weight loss, increases the rate of muscle protein synthesis,[13,14] suggesting that muscle mass loss during prolonged moderate calorie restriction is mediated by increased muscle proteolysis rather than suppressed muscle protein synthesis. The anabolic hormone insulin is able to suppress muscle proteolysis leading to a net gain of muscle protein.[15–17] In contrast, skeletal muscle insulin resistance, affecting most persons with obesity, contributes to reduced muscle mass and poor muscle quality—a phenomenon observed in sarcopenic obesity.[18,19] Improving insulin sensitivity by weight loss interventions therefore contributes to an adaptive process of muscle mass and function.[20] Interestingly, GLP-1RAs and dual GLP-1R/GIPR agonists improve insulin sensitivity through weight loss and increase first- and second-phase insulin secretion via their insulinotropic actions.[21,22] It is thus tempting to speculate that via this route, GLP-1RAs and dual GLP-1R/GIPR agonists might contribute to an adaptive effect on muscle mass and a beneficial effect on muscle health and function during weight loss. Furthermore, while studies in mice suggest that GLP-1 may have direct beneficial effects on skeletal muscle and bone,[21,23] data in humans confirming such a role are lacking and, since GLP-1Rs are not found on skeletal muscle in humans, effects on muscle must be indirect.[24] These indirect effects may include promoting skeletal muscle remodelling with exercise through increasing aerobic oxidation and mitochondrial biogenesis in skeletal muscle,[23] increasing muscle protein synthesis in postprandial hyperaminoacidaemic states,[25] increasing microvascular blood flow in skeletal muscle,[26] and improving skeletal muscle insulin resistance through body weight loss.[27]

3 | MUSCLE MASS VERSUS LEAN MASS AND GLP-1-BASED THERAPIES

Unfortunately, few studies in the weight loss literature include accurate measurements of muscle mass. Instead, commonly reported endpoints in weight loss trials include absolute and relative loss of total body lean mass (commonly assessed by dual energy X-ray absorptiometry [DXA]). Lean mass is a more inclusive measure comprising not only muscle mass but also organs, bone, fluids, and water in fat tissue. In a prior study, the proportion of weight loss from lean mass for dietary, behavioural and pharmacological weight loss (26 cohorts) ranged from 5.9% to 26.1% and the effect from surgical weight loss (29 cohorts) from 19.2% to 23.6%.[28] In a more recent systematic review and meta-analysis, bariatric surgery (10 studies involving 301 patients) showed reduction of body mass index (BMI; mean −10.8 kg/m^2) and lean mass (mean −7.4 kg), while hand grip strength was unaffected.[29] A systematic review of the effects of GLP-1RAs and sodium-glucose cotransporter-2 (SGLT2) inhibitors on humans reported that 20%–50% of total weight loss was lean mass, with similar results for both GLP-1RAs and SGLT2 inhibitors.[30] When examining the relationship between total body weight loss and lean mass loss through various weight loss interventions, it appears that the proportion of lean mass reduction per the proportion of body weight lost is highly variable but similar between dietary, GLP-1-based and surgical interventions (Figure 1). Although the magnitudes of weight loss differ among interventions (with higher magnitudes of weight loss seen with pharmacological and surgical approaches compared with dietary interventions), the slopes of the relationship for each intervention appear similar, with perhaps only a slight increase in the slope of the proportion of lean mass reduction for degree of body weight for GLP-1-based therapies. Of note, these relationships do not account for sustainability of weight loss over time and the effects of weight regain on changes in lean mass.

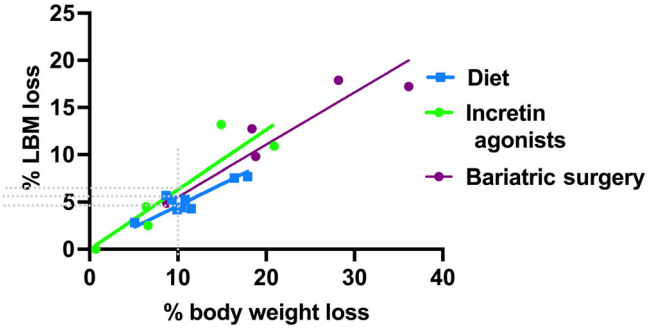


FIGURE 1 The relationship of percent weight loss to percent loss of lean body mass (LBM) resulting from dietary intervention, therapy with a glucagon-like peptide-1 receptor agonist (GLP-1RA) or a GLP-1/GIP receptor agonist, or bariatric surgery in various studies. Grey line represents the loss of LBM at a 10% weight reduction. The GLP-1RA and GLP-1/GIP RA analysis used the dataset from Table 1. Dietary interventions datasets were: PMID: 26916363; PMID: 21449785; PMID: 26187233. Surgical interventions datasets were PMID: 16608613; PMID: 17217636; PMID: 32813948. Reproduced with permission from Linge et al. Circulation. In Press.

Reductions in lean mass/volume are reported in several of the registration trials for the GLP-1RAs and related medication class in Table 1. Specifically, semaglutide has been associated with loss of lean mass of up to 40% of total weight lost[31] and liraglutide with up to 60%.[35] In the STEP-1 trial of semaglutide, lean mass was reduced by −6.92 kg or − 13.2%, with a weight reduction of −15.3 kg or −14.9%, yielding a fraction of weight lost from lean mass of 45.2%.[1] Similarly, in the SURMOUNT-1 trial of tirzepatide, lean mass was reduced by −5.67 kg or −10.9% from baseline, with a weight reduction of −22.1 kg or −20.9% (with the highest dose), yielding a

TABLE 1 Summary of glucagon-like peptide-1 receptor agonist effects on lean mass/volume in randomized clinical trials.

Pharmacological agent	Population	Measurement	Body weight change from baseline in kg or litres (%)[d]	Lean change from baseline in kg (%)	Fraction lost (or gained) of lean mass/volume as a proportion of total weight loss (%)
Semaglutide (STEP-1)[1]	BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 + comorbidity No diabetes	DXA (lean mass)	−15.3 (−14.9%)	−6.92 (−13.2%)[a]	−45.2%[a]
Semaglutide (SUSTAIN-8)[31]	Type 2 diabetes	DXA (lean mass)	−5.3 (−6.0%)[a]	−2.3 (−4.5%)[a]	−43.4%[a]
Tirzepatide (SURMOUNT-1)[2]	BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 + comorbidity No diabetes	DXA (lean mass)	−22.1 (−20.9%)[b]	−5.67[e] (−10.9%)	−25.7%[e]
Liraglutide + lifestyle (Neeland)[32,33]	BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 + metabolic syndrome No diabetes	MRI (lean volume)	−6.75 (−6.6%)	−1.02 (−2.5%)[c]	−15.0%[a]
Liraglutide (Lundgren)[34]	BMI ≥32 kg/m^2 No diabetes	DXA (lean mass)	−0.7 (−0.7%)[a]	0.0 (0.0%)[a]	0.0%[a]
Liraglutide + exercise (Lundgren)[34]			−3.4 (−3.5%)[a]	0.5 (+0.8%)[a]	+14.7%[a]

Abbreviations: BMI, body mass index; DXA, dual energy x-ray absorptiometry; MRI, magnetic resonance imaging.
[a]Value back calculated using reported mean baseline and mean absolute change.
[b]Value reflecting maximum mean observed change reported (15 mg dose).
[c]Total body lean mass estimated from MRI lean volume measured between knees and vertebra T9 according to published association and equation (PMID: 29581385).
[d]DXA measurements are mass in kilograms and MRI measurements are volume in litres.
[e]Estimated using maximum mean observed weight change reported (15 mg dose).

fraction of weight lost from lean mass of 25.7%.[2] In a SUSTAIN-8 substudy of semaglutide, patients with type 2 diabetes had a lean mass reduction of −2.3 kg or −4.5% with a weight reduction of −5.3 kg or −6.0%, yielding a fraction of weight lost from lean mass of 43.4%, but lean mass as a proportion of the whole (lean+fat) actually increased by 1.2% from baseline.[31] In contrast to these findings, a study comparing semaglutide 1 mg and tirzepatide with placebo in patients with type 2 diabetes showed lean mass reductions of approximately 15% or less of total weight loss across all groups.[36] Similarly, other studies do not show exaggerated lean mass loss with GLP-1RA treatment.[37,38] There are several potential reasons for the heterogeneity in the reported effects of GLP-1RAs on lean mass changes in clinical trials. These include the specific, individual physiological effects of different molecules, heterogeneity in dosing leading to different weight loss kinetics, varying duration of studies, methodological heterogeneity and bias in lean mass assessments, different patient populations (e.g., with vs. without diabetes), and different lifestyle interventions concomitantly prescribed with the pharmacological intervention.

Furthermore, understanding effects on a patient's muscle health from a lean mass (rather than muscle mass) assessment is challenging, as changes in lean mass may not always reflect changes in muscle mass. Indeed, research has shown that lean mass composition correlates with body weight and varies greatly among individuals.[39] In addition, up to 15% of adipose tissue can actually consist of fat-free mass (FFM; which largely consists of lean mass), meaning a large loss of adipose tissue could significantly (and variably) contribute to the overall lean mass loss and inaccurately reflect changes in muscle mass in weight loss trials.[39,40] There is a widely cited 'rule' stating the expected loss of FFM for a given amount of body weight loss that is commonly used as a reference for lean mass loss. This rule, called the quarter FFM rule, states that approximately one-quarter of weight loss will be FFM (i.e., $\Delta FFM/\Delta Weight = \sim 0.25$), with the remaining three-quarters being fat mass. In other words, when an individual loses weight purposefully, it is assumed that approximately 75% of weight is lost as fat mass, and 25% of weight is lost as FFM. However, an in-depth review of the quarter FFM rule concluded that the rule is at best an approximation, with limited mechanistic basis and questionable accuracy, as the proportion of weight lost as lean tissue varies over time and is determined by multiple factors including level of energy intake, diet composition, sex, baseline adiposity, presence of inactivity or type and level of added activity, and potentially the subject's metabolic state or hormonal response.[41] This observation, together with the variable results of the effects on lean mass from different obesity interventions, leaves us without a proper reference for what should be considered a clinically important amount of lean mass loss during weight loss. Therefore, given the current body of evidence, the clinical significance of the GLP-1-based effects on muscle mass (distinct from lean mass) remains unclear.

Unfortunately, these data may not be readily available in the near future. According to the US Food and Drug Administration (FDA) guidelines[42] for assessing weight management therapies, the only

acceptable primary efficacy endpoints for weight loss drug trials are those related directly to changes in body weight. Body composition metrics such as muscle mass or lean mass, by contrast, are considered safety endpoints, which require far smaller cohorts for testing. This is the reason why many Phase 3 clinical trials of antiobesity medications do not assess muscle/lean mass changes and those that do use a less accurate tool (DXA), rather than magnetic resonance imaging (MRI), in a subset of the overall trial population. The FDA suggests that only a fraction of participants in Phase 3 trials ought to undergo body composition assessment and the FDA does not require any tests of muscle function, mobility, or strength. Investigations into body composition or muscle-related changes associated with GLP-1RAs are thus limited and likely underpowered and, consequently, the effect on muscle health and function is largely unknown. Ultimately, the main concern when monitoring weight loss-induced changes in body composition is ensuring maintained or improved muscle health, and several approaches (including new technological advances) are in development to better characterize muscle health and function for use in weight loss studies, as described below.

4 | SARCOPENIA, OBESITY, AND WEIGHT LOSS

The most feared complication of loss of muscle mass, strength, and function in weight loss is termed sarcopenia. Sarcopenia is a loosely defined condition which is more prevalent in older adults but often exacerbated by chronic comorbidities (e.g., cardiovascular diseases, chronic kidney disease, and cancer).[16] Signs and symptoms include weakness, fatigue, loss of energy, balance problems, and trouble walking and standing. Muscle loss or weakness can lead to falls, broken bones, and other serious injuries and can affect a person's ability to care for oneself. Sarcopenia is associated with faster disease progression, higher risk of mortality and falls, and reduced quality of life.[16] The rate of muscle loss with ageing may depend on the age of the patient but is also highly affected by the severity of their disease. Research has shown that metabolic disorders, such as diabetes may be associated with an accelerated ageing process, and more rapid wasting is commonly seen within severe disease such as chronic kidney disease and heart failure.[43–45] Thus, older age, getting little or no exercise, poor nutrition, and severity of disease may increase the risk of sarcopenia. Patient characteristics such as these may influence the selection of appropriate candidates for weight loss therapies, such as GLP-1RAs, due to higher risk for clinically significant sarcopenia and impaired muscle function at baseline. Therefore, maintaining muscle health is of paramount importance to maintaining physical function in persons with overweight or obesity desiring at least modest weight loss.

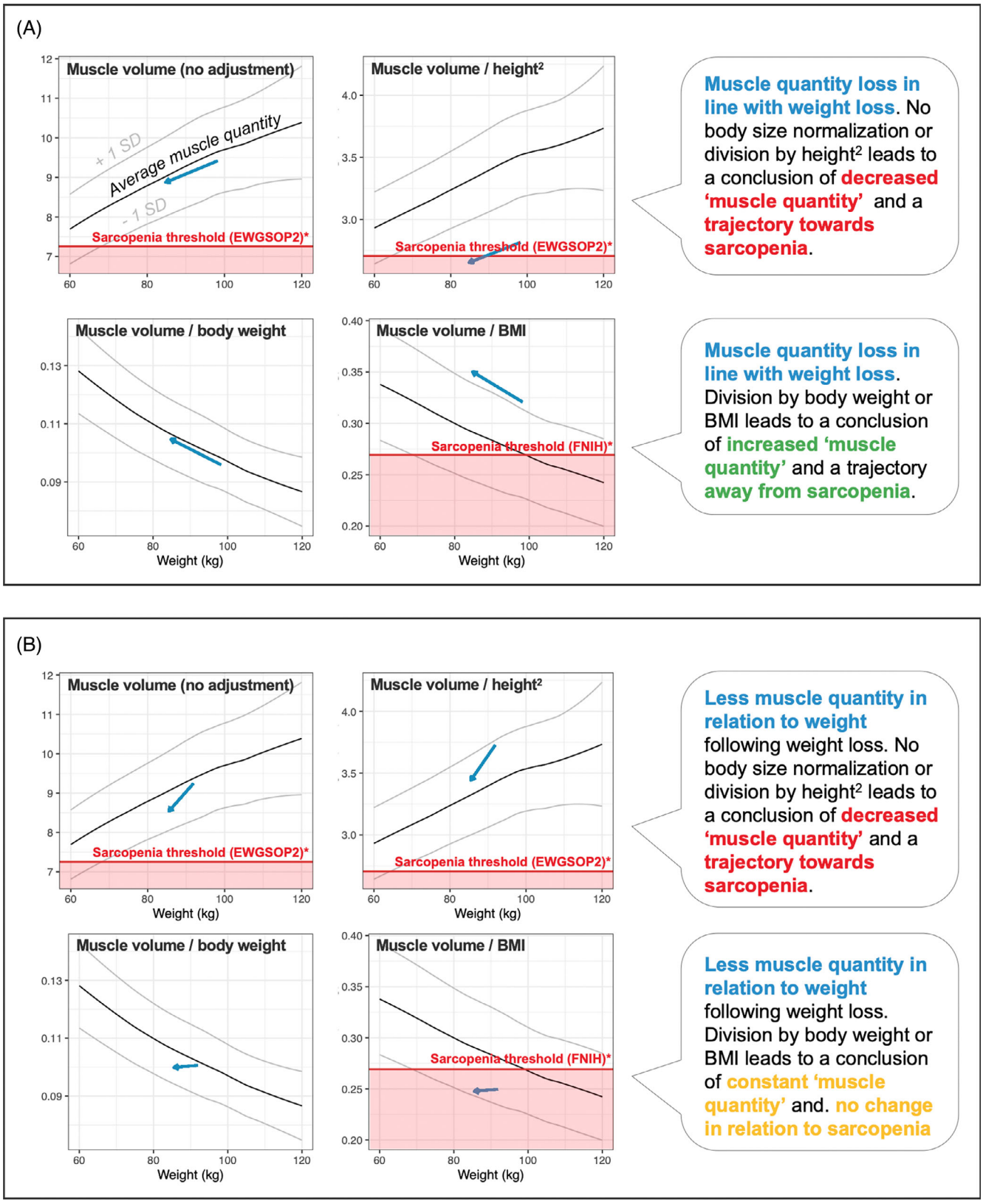
All regional working groups on the definition of sarcopenia have moved from recommending using lean mass alone to adding muscle strength and function, and switching the focus of the definition from lean mass to muscle strength and function.[46–48] The Sarcopenia Definitions and Outcomes Consortium (SDOC) has gone the furthest by including in their position statement that 'lean mass measured by DXA should not be included in the definition of sarcopenia'.[48] The reason for the shift in focus is the aforementioned heterogeneity in the association of lean mass with mortality, muscle function, and mobility limitations.[48–52] Some studies suggest that the predictive value of lean mass is limited and the focus should be on muscle strength and function instead; whereas others recognize a link between the amount of active muscle tissue and adverse outcomes, but that this relationship is obscured by the fact that lean mass is too confounded and does not accurately measure muscle mass.[49,51,53]

Although there is little consensus agreement on the thresholds in muscle quantity or quality to define sarcopenia, the field is even further from defining and understanding sarcopenic obesity (currently characterized by the co-existence of obesity and sarcopenia).[54] Depending on the definition applied, sarcopenic obesity prevalence can vary by a factor of 19 for men (4.4%–83.7%) and 26 for women (3.6%–94.0%) in the same cohort.[55] During weight gain, the amount of muscle may increase to compensate for the larger body habitus and, consequently, persons with obesity may not (or may much later) reach the threshold for sarcopenia as they age.[56] Therefore, the European Society for Clinical Nutrition and Metabolism and European Association for the Study of Obesity together support the need for a concept of 'relative or adequate muscle mass' to better describe sarcopenic obesity.[54] Indeed, a major reason for the variation in sarcopenic obesity prevalence is the method of adjusting muscle quantity for body size.[46,47,55,57] Commonly used adjustments (division by height^2, weight, or BMI) are not effective and lead to either underestimation (division by height^2) or overestimation (division by weight or BMI) of sarcopenia within obesity (Figure 2).[58] Without proper body size adjustment, it is challenging to make conclusions, or define endpoints, of what is an adaptive (or excess) reduction of muscle quantity during weight loss. Yet, using different adjustments, for example, division by height^2 versus BMI, can result in opposite conclusions of an individual having less muscle quantity and moving towards sarcopenia versus the same individual having more muscle quantity and moving away from sarcopenia (as illustrated by two patients treated with liraglutide plus a lifestyle intervention in Figure 2). Therefore, standardized approaches to adjustment are sorely needed to accurately assess changes in muscle quantity and quality during weight loss interventions.

5 | MUSCLE COMPOSITION AND GLP-1-BASED THERAPIES: MUSCLE VOLUME Z-SCORE AND MUSCLE FAT INFILTRATION

In order to better describe 'relative or adequate muscle mass', the concept of a personalized muscle volume z-score has been introduced, which describes how much an individual's muscle volume deviates from what is expected for people with the same sex and body size.[58] The concept is the same as that used in osteoporosis assessment, where a z-score is calculated by comparing a person's bone mineral density (BMD) to what is expected for someone of the same

sex and age. Thus, a low BMD z-score says that the person has less bone mass (and/or may be losing bone more rapidly) than is expected for their sex and age. Similarly, the personalized muscle volume z-score is sex-, height-, weight- and BMI-invariant, and is measured as number of standard deviations from the mean of a matched reference group. A value equal to zero indicates a muscle volume as expected



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given one's sex and body size, while a negative indicates less, and a positive indicates more muscle volume than expected for sex and body size. Similarly, observing a constant z-score (zero change) following treatment means that the person had the same deviation (if any) from expected muscle volume before and after the intervention, independent of their weight change (Figure 3). Accumulating evidence suggests that using the muscle volume z-score improves the association with muscle function and mobility, and is associated with morbidity and mortality.[58–61]

With more advanced imaging (MRI or computed tomography [CT]), in addition to more accurate and precise measures of muscle mass (rather than lean mass), it is also possible to achieve accurate measurements of muscle fat infiltration (indicating muscle quality). Muscle fat first became of interest in studies of muscular dystrophies, where the links of MRI-based muscle composition to muscle strength and mobility function have been extensively investigated.[62] Due to the large variability and challenges associated with standardization of functional tests, the field is now moving towards using high precision MRI-based measurements as primary endpoints for treatment efficacy, although the availability and feasibility of routine MRI assessment may limit widespread clinical use.[62–64] Although muscle fat is lesser explored outside the field of neuromuscular disorders, reported associations indicate a stronger link of muscle fat with adverse outcomes as compared with muscle quantity.[60,61,65–67] However, muscle quantity (mass/volume) and muscle fat are weakly correlated and seem to represent two different biological processes involved in muscle wasting.[58,67,68] Therefore, a combined assessment provides a more complete description of muscle health that has been shown to improve the performance in identifying high-risk individuals.[58–61,65,67,69]

Recent studies of the GLP-1RA liraglutide[32,33] and the GLP-1R/GIPR agonist tirzepatide[70,71] used MRI for muscle composition quantification and assessed changes in muscle volume z-score and muscle fat infiltration. Both studies reported reductions of muscle volume in line with what was expected when taking ageing, disease status, and achieved weight loss into account (Figure 3, Table 2). Changes in muscle volume z-score were similar for liraglutide and tirzepatide 5 mg, where similar magnitudes of weight loss were observed. Tirzepatide 10 mg and 15 mg showed larger weight loss and larger reductions in muscle volume z-score (although only significantly larger than expected for the 15-mg dose). In addition, both studies reported a reduction in muscle fat infiltration (Table 2) opposite from the effect of a natural increase in muscle fat seen with ageing in the UK Biobank (mean [SD] annualized change +0.11 [0.17] percentage points or 0.4% over 5 years).[58,72] In the liraglutide study,[33] muscle composition categories (low muscle volume only, high muscle fat only, 'normal' when neither was present, and 'adverse' when both were present) at baseline and follow-up were explored between treatment groups. In the liraglutide group, the proportion of participants with adverse muscle composition decreased from 11.0% to 8.2% over follow-up, despite the finding that the decline in the proportion of participants with only high muscle fat (23.3%–20.6%) was less than the increase in the only low muscle volume group (8.2%–17.8%). 'Normal' muscle composition was found in 57.5% of participants randomized to liraglutide and remained similar during follow-up (53.4%). In contrast, in the placebo group, normal muscle composition and adverse muscle composition remained similar during follow-up with a slight decrease in the proportion of participants with only high muscle fat (27.3%–21.8%) and a concomitant increase in the proportion with only low muscle volume (5.5%–12.7%), likely due to modest lifestyle-driven weight loss.

6 | IMPLICATIONS OF GLP-1-BASED THERAPIES FOR MUSCLE HEALTH AND MITIGATION STRATEGIES

Given the consistent association between muscle volume and body weight, a reduction in muscle volume is expected during successful weight loss with GLP-1-based therapies. The more modest effects of liraglutide and tirzepatide on muscle volume z-score indicate that the muscle volume lost is, in large part, in line with what was expected due to the observed weight loss. Concomitantly, these therapies successfully reduced muscle fat infiltration and led to a robust reduction in the proportion of participants with adverse muscle composition. This is particularly relevant considering the prognostic relevance of adverse muscle composition (high muscle fat plus low muscle volume). For example, in an analysis of over 39 000 participants enrolled in the UK Biobank, adverse muscle composition was detected in 11% of participants and associated with all-cause mortality even after accounting for grip strength.[60] The prevalence of adverse muscle composition appears higher in cardiometabolic disease states such as metabolic-associated steatotic liver disease and is similarly associated with excess morbidity with two- to threefold higher prevalence of diabetes and coronary heart disease.[59]

The improvement in muscle quality and composition with GLP-1-based therapies notwithstanding, how can the reduction in muscle

FIGURE 2 Trajectories of muscle quantity change with weight loss for two different women (Panel A [muscle volume z-score at baseline −1.29 SD with a decrease of −0.08 SD] and Panel B [muscle volume z-score at baseline +0.50 SD with decrease of −0.50 SD], respectively), visualized using muscle volume alone (upper left) and three different body size normalizations (division by height^2 [upper right], division by body weight [lower left], and division by body mass index [BMI; lower right]) including sarcopenia thresholds for 'low muscle quantity'. Curves show the association between each muscle quantity measurement and weight based on UK Biobank data. *Thresholds translated from dual energy X-ray absorptiometry appendicular lean mass to magnetic resonance imaging thigh muscle volume using sex-specific linear regression. EWGSOP2, European Working Group for Sarcopenia in Older People 2; FNIH, Foundation for the National Institutes of Health; MRI, magnetic resonance imaging; SD, standard deviations. Figure reproduced and modified (PMID: 31642894). Reproduced and adapted with permission from Linge et al. Circulation. In Press.

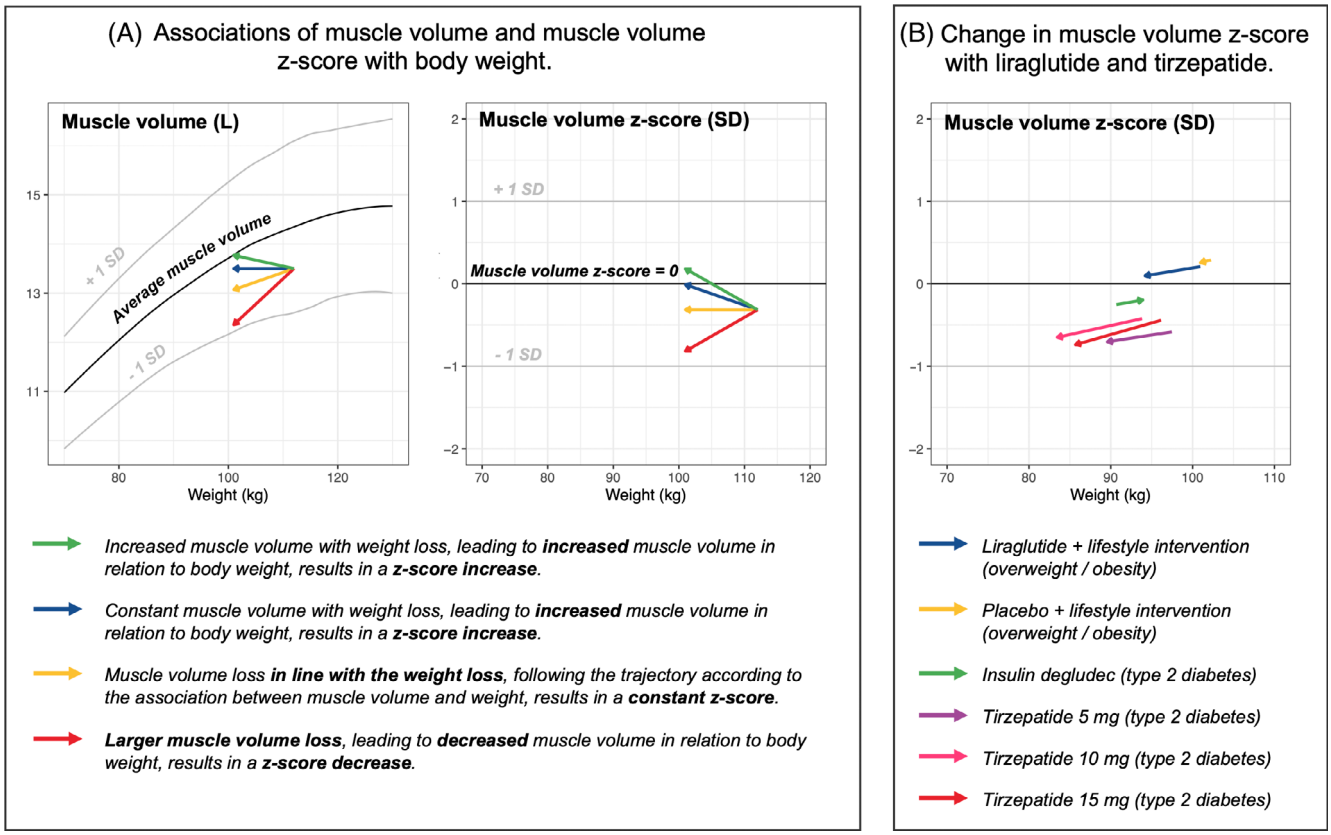

FIGURE 3 Conceptual description of how changes in muscle volume z-score with weight change relates to changes in muscle volume (in litres). Changes with body weight are shown for a man with height 1.77 m (A), and changes in muscle volume z-score with liraglutide and tirzepatide (B). SD, standard deviations. Reproduced and adapted with permission from Linge et al. Circulation. In Press.

TABLE 2 Summary of glucagon-like peptide-1 receptor agonist effects on muscle volume, muscle volume Z-score, and muscle fat infiltration quantified by MRI in randomized clinical trials.

Study description				Muscle composition change Mean (SD)		
Study	Group	Population	Weight change (%)	Muscle volume (L)	Muscle volume Z-score (SD)	Muscle vat infiltration (pp)
Liraglutide (Neeland)[32,33]	Liraglutide + lifestyle intervention	BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 + metabolic syndrome, no diabetes	−6.6	−0.35 (0.35)	−0.11 (0.31)	−0.26 (0.43)
	Placebo + lifestyle intervention		−1.2	−0.06 (0.38)	−0.03 (0.37)	−0.01 (0.58)
Tirzepatide (SURPASS-3 MRI)[70,71]	Tirzepatide 5 mg	Type 2 diabetes BMI ≥25 kg/m^2	−8.0	−0.44 (0.57)	−0.12 (0.33)	−0.23 (0.77)
	Tirzepatide 10 mg		−10.5	−0.71 (0.74)	−0.23 (0.48)	−0.42 (0.61)
	Tirzepatide 15 mg		−11.7	−0.76 (0.74)	−0.30 (0.47)	−0.44 (0.81)
	Insulin degludec		+2.3	+0.16 (0.54)	+0.06 (0.43)	+0.03 (0.40)

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide; MRI, magnetic resonance imaging; pp, percentage points. Reproduced with permission from Linge et al. Circulation. In Press.

quantity be minimized during medical (or surgical) weight loss? One way this can be achieved is by dietary modification, such as a moderate increase in protein intake. A dietary approach that includes incorporation of high protein content may preserve lean mass better than a dietary approach with lower protein content.[73] This can be especially important for older adults at higher risk for loss of muscle mass and sarcopenia.[74] Increasing protein intake is especially important for GLP-1-based treatments as there may be a shift in food preferences towards lower intake of high-nutritional quality protein compared with a standard calorie-restricted diet.[75] A high-protein diet may also reduce adaptive thermogenesis and induce a negative energy balance to help maintain weight loss in the long term.[76] Although prior data

suggested that plant-based proteins had lower protein quality, limiting muscle protein synthesis responses and potentially compromising exercise-induced gains in muscle mass, current evidence shows that plant proteins can stimulate muscle protein synthesis.[77] However, it is not clear how much protein should be recommended for consumption. Nutritional supplements which augment endogenous physiology may also be beneficial.[78] Whey proteins found in dairy products are rich in amino acids, including branched-chain amino acids, that can stimulate insulin and GLP-1 secretion, but their routine use has been limited by requiring a high dose, and consumption well in advance of a meal. New micelle technology (whey protein microgel) allowing for a more rapid absorption greater potency was recently demonstrated to significantly alter the early postprandial glucose trajectory and reduce the 2-h incremental area under the glucose excursion curve by 22% while at the same time increasing the total GLP-1 response by 66%.[79] Supplementation of branched-chain amino acids was recently shown to promote maintenance of muscle mass and improve muscle strength in post-menopausal women with sarcopenic obesity.[80] Furthermore, a randomized blinded placebo-controlled trial showed that consuming a complete nutrition drink fortified with 2.2 g eicosapentaenoic acid and 5 g branched-chain amino acids for 3 weeks increased right arm muscle mass and strength in 84 elderly individuals with inadequate protein intake.[81]

Another strategy for maintaining muscle mass during weight loss is with exercise. While both endurance and resistance-type exercise help preserve muscle mass during weight loss, resistance-type exercise has been shown to also improve muscle strength.[20] A prior systematic review demonstrated that exercise can be an effective tool to help men and women with overweight and obesity preserve FFM after moderate energy-restriction induced weight loss, which may be important for combating sarcopenic obesity in this population, especially among older adults.[82] Combining protein supplementation with resistance training exercise may further induce increases in lean body mass compared with resistance training alone in older adults.[83] There are preclinical data suggesting that GLP-1 therapy and exercise synergistically attenuate vascular inflammation and enhance metabolic insulin action in early diet-induced obesity.[84] Furthermore, GLP-1 regulates skeletal muscle remodelling to enhance exercise endurance possibly via GLP-1R signalling-mediated phosphorylation of AMPK.[23] However, the onset/worsening of fatigue associated with GLP-1-based treatment may reduce the ability of patients to perform adequate physical activity during their weight loss journey, which may have implications for muscle mass preservation. Fatigue is reported as an adverse event in GLP-1-based clinical trials approximately twofold greater than placebo although its aetiology is not fully understood and the occurrence of fatigue in the real-world setting is not well studied.

Several pharmacological treatments to maintain/improve muscle mass are under development and future directions may lead to a combination of these molecules with GLP-1-based therapies. One of the most long-standing means of increasing muscle mass is growth hormone (GH). Recombinant GH has been used in obesity with low GH levels.[85] In this condition, it only modestly reduces body weight, but improves body composition.[85] In bariatric surgery, GH slows postoperative loss of muscle mass.[86] However, it is unclear whether long-term GH replacement in the absence of GH deficiency is safe.[87] Additional targets for muscle health include the activin type II receptor (ActRII) for activin A and myostatin.[88] Both peptides negatively affect muscle mass and growth and myostatin deficiency results in increases of muscle mass in animals and humans.[89] Blockade of ActRII signalling improves body composition and metabolic parameters during calorie deficit driven by GLP-1R agonism and demonstrates the existence of Akt-independent pathways supporting muscle hypertrophy in the absence of ActRII signalling.[90] Bimagrumab is a human monoclonal antibody that binds to ActRII, preventing the action of the natural ligands. Recent studies in patients with obesity and type 2 diabetes show that, while the antibody 'only' led to a net weight loss of 6.5% after 48 weeks, it increased lean mass by 3.6% and decreased fat mass by 20.5%, with no difference in food intake.[91] High protein supplementation may further augment these drug effects: in a study of healthy volunteers with bimagrumab involving three different dosages of protein supplementation (0.4, 0.8 or 1.2 g/kg/d) over 29 days in ~20 individuals per group, treatment with bimagrumab appeared to prevent muscle loss resulting from inadequate protein intake and increase muscle mass in the setting of sufficient protein intake.[92] Further, a study of semaglutide combined with trevogrumab (anti-myostatin) and garetosmab (anti-activin A) in primates with obesity showed a large fat mass loss with an increase of lean mass.[93] Other targets, such as urocortin (Ucn)2 and Ucn3 are currently in the pipeline in preclinical models.[94] Thus, a combination of targets for muscle health with GLP-1-based treatments that reduce food intake appear to be an intriguing option to create therapies that potentially reduce fat mass while increasing muscle mass and, in theory, induce more sustainable weight loss through maintenance of metabolism/metabolic rate.

7 | CONCLUSIONS

In conclusion, it is challenging to make statements, or define endpoints, for what is an expected (or excessive) reduction of muscle quantity during weight loss, especially in the light of the highly variable results reported on lean mass effects from GLP-1RA-based treatments. However, based on contemporary evidence with the addition of MRI-based studies, skeletal muscle changes with GLP-1RA treatments appear to be adaptive: changes in muscle volume z-score indicate a change in muscle volume that is commensurate with what is expected given ageing, disease status, and weight loss achieved, and the improvement in insulin sensitivity and muscle fat infiltration likely contributes to an adaptive process with improved muscle quality, lowering the probability for loss in strength and function. Several pharmacological treatments to maintain or improve muscle mass are under development and future directions may lead to a combination of these molecules with GLP-1-based therapies. Future research of GLP-1-based therapies should focus on more accurate and meaningful assessments (including more precise imaging) of muscle mass, composition, as well as function, mobility or strength to better define their impact on muscle health for the substantial numbers of patients who will likely be taking these medications well into the future.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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