



QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

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MILANIUK, Roksana, DRZEWIECKA, Aleksandra, DANISZEWSKI, Szymon, CZERNY, Izabela, SURÓWKA, Beata, PLUTA, Wioleta, TALAROWSKI, Krzysztof, TYLEC, Piotr, ŚCIUBAK, Arkadiusz, BRYL, Jakub and PACEK, Aleksandra. GLP-1 receptor agonists and skeletal muscle: The risk of sarcopenic obesity and the role of resistance training. A narrative review. *Quality in Sport*. 2026;69:74557. <https://doi.org/10.12775/QS.2026.69.74557>

ARTICLE TIMELINE

Received: 22.07.2026. Revised: 15.08.2026. Accepted: 16.08.2026. Published: 20.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences). Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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GLP-1 receptor agonists and skeletal muscle: The risk of sarcopenic obesity and the role of resistance training. A narrative review

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Abstract

Background. GLP-1 receptor agonists (GLP-1 RAs) and incretin-based co-agonists have transformed the management of obesity and type 2 diabetes, producing weight loss approaching that of bariatric surgery. Attention has shifted from the quantity of weight lost to its quality - the proportion of fat versus skeletal muscle (lean) mass removed. A meaningful fraction of GLP-1 RA-induced loss is lean tissue, raising concern that these agents may unmask or aggravate sarcopenic obesity

Aim. To synthesise evidence on GLP-1 RAs' effect on skeletal muscle and body composition, characterise the risk of sarcopenic obesity, and appraise resistance training, nutritional and pharmacological countermeasures.

Material and methods. A review used PubMed and Google Scholar. RCTs, observational studies, reviews, meta-analyses and relevant preclinical research published in English between 2018 and 2026 were analysed.

Results. Absolute lean-mass reductions represent ~20-40% of total weight lost. Contemporary imaging suggests these changes are largely adaptive - commensurate with weight loss - rather than pathological. Principal drivers are reduced energy and protein intake from appetite suppression, catabolic drive, inactivity and anabolic resistance, not direct toxicity. Resistance training with adequate protein (~1.2-1.6 g/kg/day) is the best-established preservation strategy, and activin/myostatin blockers (e.g. bimagrumab) reduce lean-mass loss in early trials. A meta-analysis of tirzepatide trials reported improved physical function versus placebo.

Conclusions. Skeletal-muscle loss is a real, quantifiable consequence of GLP-1 RA therapy, though heterogeneous and often adaptive. Older adults, patients with type 2 diabetes, peri- and postmenopausal women, and those with low baseline muscle mass are at greatest risk. Structured resistance training with optimised protein should accompany therapy in at-risk patients; muscle-preserving pharmacotherapy is a rapidly evolving frontier.

Keywords: GLP-1 receptor agonists; semaglutide; tirzepatide; skeletal muscle; sarcopenic obesity; resistance training; body composition.

Introduction

Obesity is a chronic, relapsing disease that has reached pandemic proportions and is a major driver of cardiovascular, metabolic and oncological morbidity worldwide. Obesity is associated with a shorter life expectancy and is a major risk factor for many of the most common and economically burdensome chronic diseases. These include hypertension, type 2 diabetes mellitus, coronary artery disease, stroke, nonalcoholic fatty liver disease, and chronic kidney disease [9]. Its rising prevalence imposes an enormous clinical and economic burden and has intensified the search for effective, durable and scalable treatments. Against this background, the past decade has witnessed the emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) as a genuinely transformative class of anti-obesity pharmacotherapies.

Mechanistically, GLP-1 RAs act on receptors in the central nervous system and gastrointestinal tract to enhance glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying and, most importantly for body weight, powerfully reduce appetite and energy intake. Agents such as liraglutide and semaglutide, together with the dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist tirzepatide and the triple GLP-1/GIP/glucagon agonist retatrutide, induce weight loss on the order of 15–24%, alongside favourable effects on blood pressure, glycaemia and lipids [3,8,9].

As the magnitude of achievable weight loss has grown to approach that of bariatric surgery, the clinical conversation has shifted from how much weight is lost to what kind of tissue is lost. All effective weight-loss interventions reduce both fat and lean tissue to some degree, and a certain amount of fat-free-mass loss is an obligatory physiological consequence of reducing body size [10]. The concern is that, because GLP-1 RAs produce rapid and substantial weight loss largely through appetite suppression, a clinically important fraction of the lost mass may be skeletal muscle, potentially unmasking or accelerating sarcopenic obesity - particularly in older or metabolically vulnerable patients [3].

This distinction matters. Skeletal muscle is not merely a determinant of strength and mobility; it is a central regulator of glucose disposal, resting energy expenditure and metabolic resilience. Higher muscle mass is associated with greater longevity, and low muscle mass predicts adverse metabolic and functional outcomes [11,12]. Loss of muscle may therefore erode some of the

very metabolic benefits that GLP-1 RA therapy is intended to deliver and may predispose to weight regain - frequently as fat - once therapy is discontinued.

Aim of the review. The aim of this narrative review is threefold:

1. to synthesise current evidence on how GLP-1 RAs affect skeletal muscle and overall body composition, including how that composition is measured and interpreted;
2. to place these changes in the context of the contemporary definition of sarcopenic obesity and to identify the patients at greatest risk; and
3. to critically appraise resistance training, nutritional optimisation and emerging pharmacological agents as strategies to preserve muscle during incretin-based weight loss.

1. Material and methods

A narrative review methodology was applied in this study. A structured literature search was performed in PubMed, Scopus and Google Scholar for English-language publications between 2015 and 2026. Search terms were combined using Boolean operators and included: "GLP-1 receptor agonist", "semaglutide", "tirzepatide", "liraglutide", "retatrutide", "lean body mass", "skeletal muscle mass", "appendicular lean mass", "body composition", "D3-creatine dilution", "sarcopenia", "sarcopenic obesity", "resistance training", "protein intake", "physical function", "myostatin", "activin" and "muscle preservation". Titles and abstracts were screened by the authors to identify reports addressing body composition (assessed by dual-energy X-ray absorptiometry [DXA], bioelectrical impedance analysis [BIA], magnetic resonance imaging [MRI], computed tomography [CT] or D3-creatine dilution), muscle mass, muscle quality and/or physical function during GLP-1 RA or co-agonist therapy in adults. Randomised controlled trials, controlled and prospective/retrospective observational studies, systematic and narrative reviews, and relevant mechanistic or preclinical work were considered. Late-breaking conference presentations were included only where they reported primary outcomes of registered trials not yet available in peer-reviewed form, and are identified as such in the text. Reference lists of key articles were hand-searched for additional sources. Given the narrative design, no formal systematic-review protocol was registered and no quantitative pooling (meta-analysis) was performed.

2. Sarcopenic obesity: definition, diagnosis and clinical significance

Sarcopenia is now understood as a systemic disorder of skeletal muscle, characterized by the coexistence of diminished muscle mass and declining muscle strength [13]. Its diagnosis therefore depends on evaluating both of these parameters together [14]. Whereas early conceptualizations treated reduced muscle mass as the central hallmark of the condition, a growing body of evidence now favours a broader framework in which muscle strength takes

precedence as the principal marker of functional decline; within this view, compromised physical performance is regarded as a consequence of sarcopenia rather than one of its defining criteria - a shift consistent with findings indicating that muscle weakness, and not reduced mass alone, more reliably predicts unfavourable health outcomes [13,14].

Sarcopenic obesity (SO) is defined as the co-existence of excess adiposity with reduced skeletal-muscle mass and function [15]. It is increasingly recognised as a distinct clinical entity whose combined phenotype confers a worse prognosis than either obesity or sarcopenia alone, with amplified cardiometabolic risk, disability, falls and mortality [16,17].

2.1. The 2022 ESPEN/EASO consensus

In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) published the first consensus statement to standardise the definition and diagnosis of SO [15]. The consensus frames sarcopenia and obesity as separate phenotypes whose isolated definitions should not simply be superimposed; instead, it proposes a sequential pathway of screening, diagnosis and staging.

Diagnostically, assessment of skeletal-muscle function comes first (for example, handgrip strength or a sit-to-stand test), followed by assessment of body composition, where the presence of excess adiposity together with low skeletal-muscle mass confirms the diagnosis [15]. A methodologically important feature is that skeletal-muscle mass is adjusted to body weight rather than to height squared, distinguishing SO criteria from those used for isolated sarcopenia. Confirmed cases are staged as stage I (no clinical complications) or stage II (complications attributable to altered body composition or muscle dysfunction).

Population studies applying these criteria - for example the German KORA-Age cohort - confirm that SO is prevalent in older adults and is associated with multimorbidity, disability, polypharmacy and cognitive impairment [17], while analyses in older women link ESPEN/EASO-defined SO to an increased risk of falls and adverse bone-mineral-density outcomes [16]. The consensus explicitly encourages secondary analysis of existing datasets and prospective studies to evaluate the predictive value and treatment responsiveness of this definition - a call directly relevant to the GLP-1 RA era.

2.2. Why muscle matters during weight loss

Muscle mass is a principal determinant of resting energy expenditure and insulin-mediated glucose uptake, and higher muscle mass index has been associated with greater longevity in older adults [11,12]. Any weight-loss intervention that removes muscle without a corresponding improvement in muscle quality or function therefore risks tipping a patient with borderline reserve into overt sarcopenic obesity.

2.3. The bone dimension: towards osteosarcopenic obesity

Muscle does not decline in isolation. Rapid weight loss with incretin-based therapy is also accompanied by reductions in bone mass, and the interplay of low muscle, low bone and excess fat has been conceptualised as osteosarcopenic obesity - a phenotype of particular concern in postmenopausal women and older adults already predisposed to osteoporosis [16]. Evidence on bone-specific outcomes during GLP-1 RA therapy remains limited, but the potential for a combined musculoskeletal cost reinforces the case for proactive protective strategies and for monitoring that extends beyond the number on the scale [18].

3. Assessing body composition: methods and interpretation

Interpreting the muscle effects of GLP-1 RAs requires understanding how body composition is measured, because much of the apparent controversy in the literature stems from methodological differences rather than genuine biological disagreement [10].

Dual-energy X-ray absorptiometry (DXA) is the most widely used reference method in clinical trials; it partitions the body into fat mass, bone mineral and lean (fat-free) soft tissue, but it measures fat-free mass rather than skeletal muscle specifically, so a proportion of measured lean-mass change reflects water, organ and connective tissue rather than contractile muscle [10]. Bioelectrical impedance analysis (BIA) is inexpensive and accessible but is sensitive to hydration status and less precise. Magnetic resonance imaging (MRI) and computed tomography (CT) can quantify skeletal-muscle volume and intramuscular fat directly and are considered the most accurate for muscle quality, but are costly and rarely used at scale.

A crucial conceptual point is that a decline in fat-free mass is, in part, an obligatory and physiologically appropriate accompaniment to a reduction in overall body size; the relevant question is not whether lean mass falls but whether it falls more than expected for the magnitude of weight loss, and whether function is preserved [10]. To address this, contemporary analyses express muscle change as a z-score relative to a demographic reference. Using MRI-based muscle-volume z-scores, Linge et al. [2] argued that skeletal-muscle changes with GLP-1 RA treatment are, at a population level, largely adaptive - commensurate with what would be expected for the degree of weight loss - rather than pathologically excessive. This interpretive framework helps reconcile the alarming-sounding absolute figures with a more measured clinical reading, while still acknowledging that individual, high-risk patients may lose disproportionate and functionally meaningful muscle.

A second, and arguably more fundamental, caveat concerns what these instruments actually quantify. Direct measurement of muscle can diverge sharply from its imaging proxies: in a pilot

study nested within a geriatric weight-loss trial, every DXA- and computed tomography-derived body-composition metric declined significantly, yet whole-body skeletal muscle mass measured directly by D3-creatine dilution was unchanged, and grip strength improved [19]. This dissociation is consistent with broader evidence that D3-creatine-derived muscle mass, rather than DXA lean mass, is the measure that tracks functional capacity and adverse outcomes in older adults [20]. Applied to the incretin literature, it implies that the widely quoted lean-mass loss fractions may materially overstate the loss of contractile tissue, and it reinforces the case for pairing composition data with functional testing [10,21].

4. GLP-1 receptor agonists and body composition: the evidence

Reductions in lean mass are consistently reported across the registration trials of the GLP-1 RA class, though the reported magnitude varies substantially with the agent, the population and the measurement method [3,4,18].

4.1. Semaglutide and older GLP-1 RAs

Exploratory body-composition analyses of pivotal semaglutide trials indicated that a substantial share of the weight lost was fat-free mass. In the STEP 1 trial, semaglutide produced significantly greater reductions in both fat mass and lean body mass than placebo [22], and systematic appraisals place the lean-mass fraction at up to approximately 40% of total weight lost with semaglutide, with an even higher fraction reported for the less potent, shorter-acting liraglutide [3,23,24]. Dedicated DXA-based studies - DXA being the reference standard - remain relatively few, and existing data are heterogeneous in method and reporting [4].

4.2. Tirzepatide (SURMOUNT-1 DXA substudy)

The dual GLP-1/GIP agonist tirzepatide provides some of the most robust body-composition data. In the DXA substudy of SURMOUNT-1 (160 participants completing baseline and week-72 scans), tirzepatide produced changes from baseline of - 21.3% in body weight, - 33.9% in fat mass and - 10.9% in lean mass, compared with - 5.3%, - 8.2% and - 2.6% respectively with placebo (all $p < 0.001$) [1]. Expressed as a proportion, approximately 75% of the weight lost was fat mass and 25% lean mass - a ratio broadly consistent across subgroups defined by sex, age and degree of weight loss, and comparable to placebo [1]. Complementary imaging data suggest reductions in muscle fat infiltration with relatively preserved fat-free muscle volume, pointing to improved muscle quality alongside modest quantity loss [1,2].

4.3. Retatrutide and the co-agonist frontier

The triple GLP-1/GIP/glucagon agonist retatrutide has produced the largest weight losses reported to date for a pharmacological agent, exceeding 24% at higher doses over 48 weeks [9]. With greater total weight loss comes a correspondingly greater absolute reduction in fat-free

mass, making the question of muscle preservation even more pressing for this next generation of agents, for which detailed, function-inclusive body-composition data are still maturing [3].

4.4. Putting the numbers in perspective

Integrating across the class, incretin-based therapies predominantly reduce adipose tissue - including visceral and ectopic depots - but also produce absolute reductions in lean mass that meta-analyses place at roughly 20-40% of total weight loss, with estimates across the class ranging from about 15% to 45% [2,3]. Commentators have observed that the absolute magnitude of lean-mass loss (on the order of ~10%, or roughly 6 kg) can approximate that accrued over a decade or more of ageing [3] - a comparison that, while attention-grabbing, must be interpreted alongside the concurrent, and often larger, loss of harmful fat mass, and against the adaptive framework described above [2,10]. Crucially, current studies remain constrained by methodological heterogeneity, small substudy sample sizes and infrequent assessment of functional outcomes, so the extent to which measured lean-mass loss translates into weakness or frailty is still incompletely defined [1]. Where function has been measured, however, the picture is more reassuring than the mass data alone imply: a systematic review and meta-analysis of randomised trials of tirzepatide 10 and 15 mg found improved patient-reported physical function relative to placebo [7]. That these outcomes were self-reported rather than performance-based (for example grip strength or gait speed) remains an important limitation [21].

Table 1. *Body-composition outcomes of incretin-based therapies across key trials.*

Agent (trial)	Method	Duration	Weight change	Lean-mass change	Ref.
Semaglutide 2.4 mg (STEP 1)	DXA substudy	68 weeks	-14.9%	Significant reduction vs placebo	[22]
Tirzepatide (SURMOUNT-1)	DXA substudy (n = 160)	72 weeks	-21.3%	-10.9% (~25% of weight lost)	[1]
Retatrutide (phase 2)	Trial report	48 weeks	>24% (highest dose)	Data still maturing	[9]
Semaglutide + bimagrumab (BELIEVE)	DXA	After 48 weeks	-16.4%	Lean mass largely preserved	[6]

5. Mechanisms of muscle loss during GLP-1 RA therapy

A recurring theme in the literature is that GLP-1 RAs do not appear to be directly myotoxic; rather, muscle loss is largely an indirect consequence of the energy-deficit state these drugs create [3]. Several overlapping mechanisms have been proposed.

- **Reduced energy and protein intake.** The dominant mechanism is decreased food intake. When appetite is strongly suppressed, total intake falls and protein intake tends to decline disproportionately, because protein-rich foods require more deliberate effort to consume [3,4]. Inadequate protein availability limits muscle protein synthesis, while the caloric deficit increases reliance on endogenous (including muscle) protein for energy.
- **Physical inactivity.** Reduced mechanical loading of muscle - compounded by early gastrointestinal side-effects, nausea and fatigue during dose escalation - removes a key anabolic stimulus and accelerates atrophy [3].
- **Anabolic resistance.** Particularly in older adults, the muscle protein-synthetic response to dietary amino acids and to exercise is blunted (anabolic resistance), lowering the efficiency with which available protein is converted into muscle and amplifying the impact of reduced intake [25].

Set against these catabolic pathways, emerging evidence suggests GLP-1 signalling may exert modest protective effects on muscle quality. In preclinical work, semaglutide-induced weight loss improved mitochondrial energy efficiency in skeletal muscle [26], consistent with the imaging finding of reduced intramuscular fat and improved muscle composition. This has fuelled an ongoing debate about whether the lean-mass loss observed with GLP-1 RAs is maladaptive (adversely affecting muscle health or function), adaptive (a physiological, largely benign accompaniment to weight loss) or occasionally even net-beneficial for muscle quality [2]. The pragmatic resolution is that moderate lean-tissue decline can reasonably be regarded as a physiological component of body-composition change unless accompanied by demonstrable functional deterioration [3].

6. Who is at risk? High-risk populations

The clinical significance of GLP-1 RA-associated muscle loss is not uniform; it is concentrated in patients whose baseline reserve is limited or whose physiology magnifies catabolism.

- **Older adults.** Age-related sarcopenia and anabolic resistance compound rapid weight-loss-induced muscle loss, so that lean-mass reductions may translate more readily into falls, weakness and impaired mobility. Reviews of GLP-1 RA use in older adults highlight the risk

of sarcopenia and sarcopenic obesity and recommend integrating tailored resistance exercise and adequate protein intake with therapy [25,27].

- **Patients with type 2 diabetes.** Hyperglycaemia, impaired insulin signalling, accumulation of advanced glycation end-products and chronic low-grade inflammation independently promote muscle degradation, so diabetes both raises baseline sarcopenia risk and may accentuate treatment-related loss; nutritional deficiencies during therapy may further compound this [3,4].

- **Peri- and postmenopausal women.** The decline in oestrogen - an anabolic hormone that helps maintain muscle and bone - accelerates midlife musculoskeletal loss, and this population is heavily represented among GLP-1 RA users [4,16].

- **Low baseline muscle mass and sedentary individuals.** Those with limited muscular reserve or habitually low activity and protein intake are most likely to experience disproportionate, clinically meaningful muscle loss [3].

Identifying these groups before initiating therapy allows anticipatory, proactive muscle-preservation strategies rather than reactive management after functional decline has occurred [27].

7. Strategies to preserve muscle health

Because muscle loss during GLP-1 RA therapy is predominantly an **indirect** consequence of energy and protein deficit, inactivity and anabolic resistance - rather than direct myotoxicity - it is, in principle, largely preventable [3].

7.1. Resistance training

Resistance (strength) training is a well-established stimulus for maintaining muscle mass, muscle function, basal metabolic rate and glycaemic control across diverse populations, and it reliably preserves muscle mass during diet-induced weight loss [3]. Its role specifically during incretin-based weight loss is biologically compelling but, as yet, incompletely proven by dedicated trials.

A systematic review and meta-analysis in obese older adults demonstrated that resistance training prevents the muscle loss otherwise induced by caloric restriction [5], establishing the principle in the population most vulnerable during GLP-1 RA therapy. The most relevant drug-specific bridging evidence comes from liraglutide: Lundgren et al. [28] demonstrated that adding a structured exercise programme to liraglutide, following an initial low-calorie-diet phase, preserved fat-free mass and potentiated fat-mass loss, supporting a combined

pharmacological-plus-exercise strategy. Supervised, structured exercise appears more effective than simple advice to exercise in limiting muscle loss during incretin therapy [23].

To date, however, no completed randomised trial has definitively isolated the effect of resistance training added to modern potent GLP-1 RAs such as semaglutide or tirzepatide [3]. This evidence gap is now being addressed prospectively: the LEAN-PREP trial, a single-centre, six-month randomised controlled trial, will allocate 232 adults with obesity (1:1:1:1) to control, resistance exercise, protein supplementation (targeting 1.6 g/kg/day) or combined resistance exercise plus protein, alongside semaglutide or tirzepatide therapy; the primary outcome is MRI-measured quadriceps cross-sectional area, with DXA body composition, strength and physical function among the secondary outcomes [29]. Trials of this design will be central to converting mechanistic plausibility into guideline-grade recommendations.

7.2. Practical exercise prescription

Pending definitive trial data, expert and consensus guidance recommends structured, progressive resistance training as a routine adjunct to GLP-1 RA therapy, especially in higher-risk patients [4,27]. A pragmatic prescription comprises two to three sessions per week targeting all major muscle groups, using multi-joint exercises performed for roughly 2–4 sets of 8–12 repetitions at a moderate-to-hard intensity, with gradual (progressive) increases in load as strength improves. Because trials advised substantial weekly activity (on the order of 150–240 minutes combining aerobic and resistance work) that was often poorly monitored, emphasis should be placed on supervision and adherence rather than volume alone [23]. Resistance training should ideally be combined with adequate protein intake, reflecting the synergy between mechanical loading and amino-acid availability in stimulating muscle protein synthesis [5]. Because adherence, rather than prescription, is usually the limiting factor, telemedicine-based and digital-health-delivered exercise programmes are emerging as a promising route to scalable, supervised training during pharmacological weight loss [21].

7.3. Nutritional strategies

Because reduced and protein-poor intake is the principal driver of muscle loss during GLP-1 RA therapy, deliberate nutritional management is a cornerstone of muscle preservation. Consensus and expert guidance recommend a protein intake greater than 1.2 g/kg/day - commonly framed as 1.2–1.6 g/kg/day - distributed evenly across meals and combined with aerobic activity and structured resistance training [4,27]. Even distribution matters because per-meal protein thresholds must be reached to maximally stimulate muscle protein synthesis, a requirement made harder to meet by appetite suppression and early satiety.

Protein and amino-acid quality (including adequate leucine) is also relevant, particularly against a background of anabolic resistance in older adults [25]. Beyond protein, attention to overall dietary adequacy - including fibre, vitamins and minerals relevant to muscle and bone health - helps offset the nutrient shortfalls that can accompany markedly reduced intake [4]. Practically, dietary counselling during the dose-escalation phase serves a dual purpose: it supports protein and micronutrient targets and simultaneously mitigates the mild-to-moderate gastrointestinal symptoms that otherwise reduce intake and adherence. Periodic monitoring of body composition (DXA or BIA) and of function (handgrip strength, sit-to-stand) allows nutritional and exercise prescriptions to be individualised over time [10].

7.4. Emerging pharmacological approaches to muscle preservation

Beyond lifestyle measures, a new therapeutic frontier aims to pharmacologically decouple fat loss from muscle loss by targeting the activin/myostatin signalling pathway, a key negative regulator of muscle growth. Preclinical work established the principle: antibody blockade of activin type II receptors preserved skeletal-muscle mass and enhanced fat loss during GLP-1 receptor agonism in animal models [30].

This concept has now been tested in humans. Bimagrumab, a first-in-class monoclonal antibody that blocks activin type II receptors and thereby promotes muscle preservation and growth, was evaluated alone and with semaglutide in the phase 2 BELIEVE trial [6]. The combination produced substantial weight loss while markedly shifting its composition toward fat: in the higher-dose combination arm, the great majority of the weight lost was fat mass, and lean mass was largely preserved - a body-composition profile not previously seen with semaglutide or tirzepatide alone. Bimagrumab monotherapy actually increased lean mass, and the combination reduced visceral fat and waist circumference substantially, with a tolerable safety profile dominated by muscle spasms (bimagrumab) and gastrointestinal effects (semaglutide) [6]. These findings provide proof of concept that the *quality* of weight loss can be pharmacologically enhanced.

More broadly, the evolution toward dual and triple incretin co-agonists (tirzepatide, retatrutide) and toward combination regimens that pair appetite-directed central mechanisms with peripheral anabolic or activin-pathway modulation - including other myostatin-pathway agents in development - signals a paradigm shift: from maximising the amount of weight lost toward optimising its composition [6,18]. Data on the body-composition effects of these co-agonists and combinations, however, remain early and require confirmation in larger, longer trials with functional endpoints.

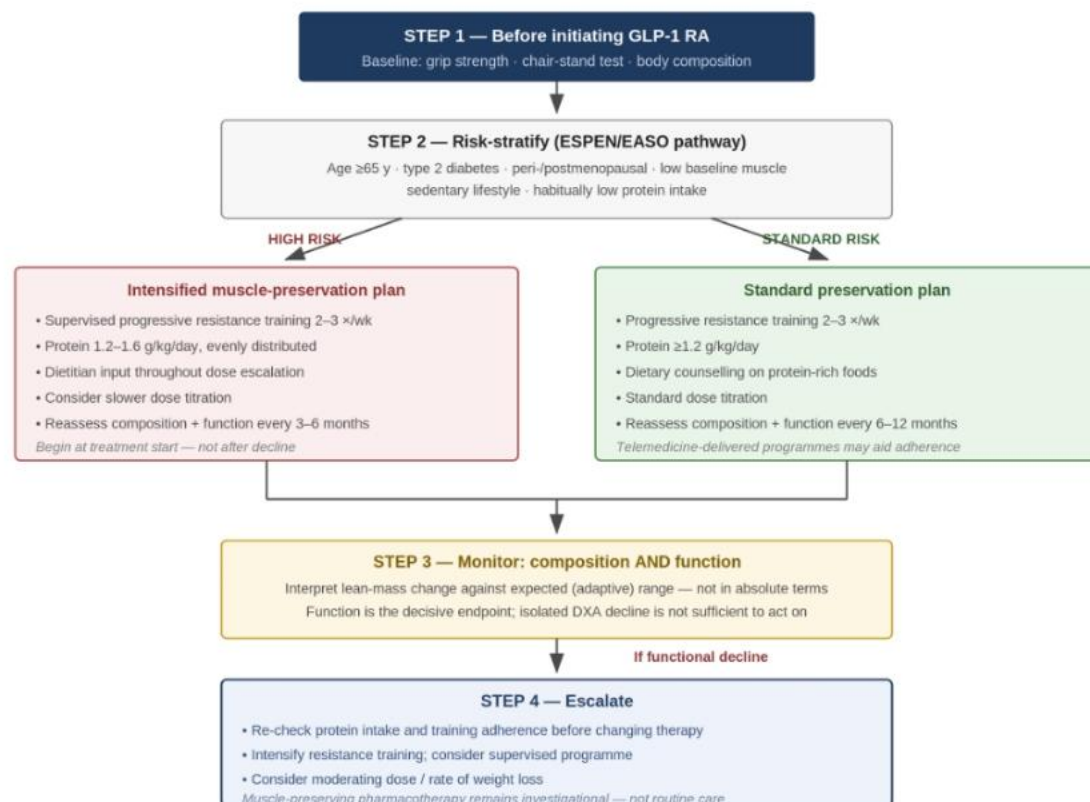


Figure 1. Proposed clinical pathway for preserving skeletal muscle during GLP-1 receptor agonist therapy. DXA, dual-energy X-ray absorptiometry.

8. Discussion

Synthesising the available evidence, muscle loss during GLP-1 RA therapy is real and quantifiable, is in most patients an adaptive accompaniment to substantial fat loss, but becomes clinically important in identifiable high-risk groups - and is largely modifiable. A pragmatic clinical approach for patients starting therapy may be summarised as follows.

- Risk-stratify before initiation. Screen for sarcopenic-obesity risk - particularly in older adults, patients with type 2 diabetes, peri-/postmenopausal women and sedentary individuals - using simple functional tests (e.g. handgrip strength, sit-to-stand) in line with the ESPEN/EASO pathway [15].
- Prescribe resistance training proactively. Recommend two to three progressive resistance sessions per week from the outset, rather than after functional decline appears [5,23].
- Optimise protein and diet. Target $\approx 1.2\text{--}1.6$ g/kg/day, evenly distributed, with dietary counselling during dose escalation to support intake, micronutrient adequacy and gastrointestinal tolerance [4,27].

- Monitor body composition and function. Where feasible, use serial DXA or BIA plus functional testing, interpreting lean-mass change against the expected (adaptive) range rather than in absolute terms alone [2,10].
- Consider emerging pharmacotherapy selectively. Muscle-preserving agents such as bimagrumab remain investigational but may become relevant for patients at highest risk of clinically significant muscle loss [6].

A further consideration is discontinuation. Because appetite suppression is not durable after stopping therapy, weight regain is common - and regained weight is typically deposited as fat rather than muscle, which can worsen body composition over repeated cycles. Establishing resistance-training and dietary habits during treatment may therefore pay dividends well beyond the treatment period itself [27,28].

9. Limitations and future directions

Several limitations temper current conclusions. Body-composition data derive from heterogeneous methods (DXA, BIA, MRI, CT) with differing precision, and many key findings come from small substudies of larger trials, limiting generalisability [1,10]. Functional outcomes - strength, gait speed, physical performance - are assessed far less often than mass, so the clinical consequences of measured lean-mass loss remain uncertain [3]. Data for the newest dual and triple co-agonists, and for muscle-preserving combinations, are still early, and no completed randomised trial has yet isolated resistance training added to modern potent GLP-1 RAs [29].

Priorities for future research include standardised, function-inclusive body-composition assessment; adequately powered trials of resistance training and protein optimisation during semaglutide/tirzepatide therapy; dedicated study of high-risk populations (older adults, type 2 diabetes, menopause); evaluation of bone as well as muscle outcomes; and longer-term study of whether muscle preservation improves weight-maintenance, metabolic and functional outcomes after therapy [4,27]. As a narrative review, the present synthesis is also subject to the selection and interpretation biases inherent to the design, and did not involve quantitative pooling.

10. Conclusions

Skeletal-muscle loss is a real, quantifiable and clinically relevant consequence of GLP-1 RA-induced weight loss, typically accounting for roughly one fifth to two fifths of total weight lost. In most patients this loss appears adaptive - commensurate with the degree of weight loss and accompanied by improved muscle quality - but it becomes clinically important in older adults,

patients with type 2 diabetes, peri- and postmenopausal women, and those with low baseline reserve. The mechanism is predominantly indirect, driven by reduced energy and protein intake, catabolic drive, inactivity and anabolic resistance rather than direct muscle toxicity. Resistance training combined with optimised protein intake is the best-established strategy to protect muscle during therapy and should be offered proactively to at-risk patients, while activin/myostatin-pathway agents such as bimagrumab herald a shift toward pharmacologically improving the quality, not merely the quantity, of weight loss. Integrating these measures into routine obesity care will be essential to ensure that the metabolic gains of the incretin era are not offset by avoidable losses of skeletal muscle and bone.

Disclosure

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

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable. All data discussed are available in the cited published sources.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used ChatGPT (OpenAI) for linguistic refinement, grammar correction, and structural editing of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the scientific content, interpretation of the data, and final version of the manuscript

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