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Preserving Skeletal Muscle and Function During GLP-1 Receptor Agonist Therapy: An Evidence-Informed Exercise Prescription Framework

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Abstract

Background & Aim: GLP-1 RAs (e.g., semaglutide) and dual GIP/GLP-1 RAs (tirzepatide) induce substantial weight loss, but ~25% derives from fat-free mass (FFM). Whether this threatens skeletal muscle remains contested. Standard guidelines offer generic resistance training advice, ignoring the drugs' gastrointestinal and behavioral side effects. This narrative review aims to synthesize mechanisms of GLP-1 RA-associated lean mass loss, critique DXA-derived FFM as a clinical endpoint, shift focus to muscle quality/function, and propose a tailored exercise and nutritional framework.

Material and Methods: Literature, guidelines, meta-analyses, and clinical trials regarding GLP-1 RA body composition, muscle physiology, training methodology, and sports nutrition were synthesized. Recommendations were graded using a 4-tier hierarchy: direct clinical evidence, indirect evidence, mechanistic rationale, and expert inference.

Results: FFM loss (~25%) is heterogeneous and method-dependent. A model of drug-associated anabolic resistance (negative energy balance, protein intake below the per-meal leucine threshold, and reduced NEAT) explains this loss without direct muscle toxicity. DXA-FFM is a biased proxy for muscle; MRI and functional data suggest muscle quality may improve despite mass declines. Four distinct clinical barriers were identified: unreliable self-assessment of gastric motility, chronic nausea/fatigue, severe appetite suppression, and a gap

in structured guidance. A framework of 20 tailored recommendations was developed (3 based on direct evidence, 17 on indirect/mechanistic data).
Conclusions: GLP-1 RA-associated muscle loss is a real, unevenly distributed risk mitigable via barrier-adapted resistance training and nutritional optimization. The proposed framework is physiologically plausible but requires prospective validation. Intervention is highly indicated for patients with low baseline muscle reserve, advanced age, prior bariatric surgery, CKD, or HFrEF.

Key words: GLP-1 receptor agonists; semaglutide; tirzepatide; sarcopenia; resistance training; muscle quality; anabolic resistance; lean body mass.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) — including semaglutide and the dual GIP/GLP-1 receptor agonist tirzepatide — have fundamentally altered the pharmacological management of obesity. Head-to-head data from the SURMOUNT-5 trial demonstrated a least-squares mean weight reduction of 20.2% with tirzepatide versus 13.7% with semaglutide at 72 weeks, corresponding to absolute losses of 22.8 kg and 15.0 kg, respectively (Aronne et al., 2025). Reductions of this magnitude, unprecedented outside of bariatric surgery, have repositioned incretin-based pharmacotherapy as a primary rather than adjunctive strategy in obesity medicine.

This efficacy, however, has surfaced a body-composition paradox that is now central to the clinical conversation around these agents. Weight lost under GLP-1 RA therapy is not exclusively adipose in origin: in the SURMOUNT-1 DXA substudy, approximately 25% of weight lost with tirzepatide was lean mass rather than fat (Look et al., 2025), a figure corroborated at a higher evidence tier by a network meta-analysis of 22 randomized controlled trials (Karakasis et al., 2025). That pooled estimate is not uniform across the drug class or across individual studies — liraglutide, for instance, appears to preserve lean mass more effectively than tirzepatide or semaglutide, a heterogeneity that remains an open research question — and it is not the last word on the matter.

Indeed, this evidence base is best characterized as contested rather than settled. A recent narrative review argues the opposing case: that relative lean-mass preservation and largely maintained resting energy expenditure indicate GLP-1 RAs do not accelerate sarcopenia at the population level (Bhandarkar et al., 2025). This position need not be wrong for the present concern to stand. Even granting relative preservation on average, an absolute lean-mass loss of roughly one kilogram per three kilograms of fat lost is not negligible once compounded over the 15–25 kg total losses now routine with tirzepatide and semaglutide, particularly in

patients with lower baseline muscle reserve. The relevant clinical question is therefore narrower and more defensible than "do GLP-1 RAs cause sarcopenia": it is whether exercise prescription can be optimized, given these drugs' distinct gastrointestinal and behavioral side-effect profile, to shift a small but real risk further in the patient's favor. Because DXA-derived lean mass itself includes body water, organs, and connective tissue rather than skeletal muscle alone, the more defensible clinical endpoint requires reconsideration (Section 3).

A second, more recent line of evidence compounds this concern. Preliminary observational data drawn from a retrospective cohort of 753 adults with obesity, using linked electronic health record and activity-tracker data from the NIH All of Us Research Program, suggest that average daily step counts and moderate-to-vigorous physical activity minutes both declined significantly following GLP-1 RA initiation, with the largest declines in men and in patients reporting joint or muscle pain (Maharjan et al., 2026). As this finding derives from a conference presentation and pre–post cohort design rather than a peer-reviewed randomized trial, it should be treated as hypothesis-generating rather than definitive; nonetheless, it raises the possibility that reduced spontaneous movement compounds pharmacologically induced anorexia to accelerate lean-tissue loss, independent of any direct catabolic effect of the drug on muscle itself.

Clinical and scientific guidance has, to date, responded to this concern in a largely generic fashion. Professional statements and narrative reviews on GLP-1 RA-associated body-composition change converge almost uniformly on the recommendation that patients should engage in resistance training to preserve lean mass. This advice is not incorrect, but it is clinically incomplete. It rarely specifies training frequency, intensity, volume, or progression; it rarely addresses how peri-workout nutrition should be adapted when protein targets of 1.2–1.6 g/kg/day are rendered impractical by profound appetite suppression; and it does not engage with the fact that a meaningful proportion of GLP-1 RA users experience delayed gastric emptying, chronic low-grade nausea, and fatigue that may directly limit their capacity to tolerate conventional resistance-training protocols developed in eucaloric, non-pharmacologically appetite-suppressed populations. The result is a prescriptive gap between what is recommended in principle and what is clinically actionable at the point of care.

The present review addresses this gap by proposing an evidence-informed exercise prescription framework organized around a conceptual model of drug-associated anabolic resistance — a synthesis of adjacent bodies of evidence rather than an established disease mechanism — in which negative energy balance, suppressed protein intake, and reduced non-

exercise activity thermogenesis are proposed to jointly blunt the muscle protein synthetic response to a given anabolic stimulus. Framing the clinical problem in this way, rather than as a list of isolated side effects, allows exercise prescription, nutritional timing, and symptom management to be organized as complementary strategies aimed at a common physiological target.

It is important to state at the outset what this review does not claim. No randomized controlled trial has, to the authors' knowledge, directly tested a resistance-training protocol specifically designed for and validated in a GLP-1 RA-treated population. The framework proposed here is therefore not presented as an optimal or validated protocol, but as a physiologically plausible clinical model, synthesized from adjacent evidence in obesity medicine and exercise physiology, that requires prospective validation before it can be considered a clinical standard. Each individual recommendation is labeled according to whether it is supported by direct evidence in GLP-1 RA-treated populations, indirect evidence extrapolated from related fields, mechanistic rationale alone, or expert inference — a transparency structure summarized in Section 7. This distinction is the organizing principle of the review, separating a clinically useful hypothesis-generating framework from an overreaching claim of practice-changing efficacy.

Accordingly, the aims of this narrative review are threefold: (1) to synthesize the mechanistic basis of GLP-1 RA-associated lean-mass loss under a proposed anabolic-resistance model; (2) to examine the limitations of DXA-derived fat-free mass as a clinical endpoint and discuss the broader construct of muscle quality and function; and (3) to propose, with explicit evidence-tier labeling, an exercise and nutritional framework tailored to the gastrointestinal and behavioral barriers this population faces, concluding with a structured agenda for the prospective research needed to test it.

2. Mechanistic Basis: A Conceptual Model of Anabolic Resistance

The term anabolic resistance did not originate in the GLP-1 RA literature. It is borrowed from the geriatric and critical-care nutrition fields, where it describes the blunted rise in muscle protein synthesis that older or critically ill patients exhibit in response to a protein or exercise stimulus that would robustly stimulate synthesis in a younger, healthy adult (Tieland et al., 2019). What is proposed here is its application to a new context: that three features of GLP-1 RA pharmacotherapy — negative energy balance, chronically suppressed protein intake, and reduced non-exercise activity thermogenesis (NEAT) — converge to produce a comparable

state of blunted anabolic responsiveness in an otherwise young, metabolically healthy population that would not, under ordinary circumstances, be expected to show it. Each contributing pathway is considered in turn below, followed by an account of where this model is strained by preclinical evidence that does not yet fit it neatly.

2.1. Negative energy balance and the myofibrillar protein synthesis / muscle protein breakdown balance

Skeletal muscle mass at any given moment reflects the net balance between myofibrillar protein synthesis (MyoPS) and muscle protein breakdown (MPB). Sustained negative energy balance — the mechanism common to every effective weight-loss intervention, pharmacological or otherwise — shifts this balance unfavorably by reducing substrate availability for synthesis, while insulin and insulin-like growth factor 1 (IGF-1) signaling, both permissive for MyoPS, decline in parallel with adiposity and caloric intake. This can be placed in context: bariatric surgery produces approximately 35% total weight loss, of which a substantial fraction is fat-free mass, while phase III trials of incretin-based pharmacotherapy achieve 15–25% weight loss accompanied by fat-free mass losses of up to 25–30% — proportionally larger relative to total weight lost than surgical series, though smaller in absolute terms given the lower total weight change (Stefanakis et al., 2024).

This pattern is consistent with a body of literature holding that the magnitude of fat-free mass loss during weight reduction tracks the magnitude and rate of the energy deficit far more closely than the specific method used to create that deficit; GLP-1 receptor agonists induce loss of lean mass, but so does caloric restriction of comparable severity. This reframing matters for how the apparent paradox in Section 2.4 is resolved: if lean-mass loss is substantially a function of deficit size and rate rather than a GLP-1-specific catabolic action, then the exercise and nutritional countermeasures proposed later are not correcting a unique drug toxicity — they are countering the same energy-deficit-driven MyoPS/MPB imbalance that any sufficiently aggressive weight-loss intervention would produce, applied to a population whose ability to counteract it is unusually constrained by gastrointestinal side effects.

2.2. Suppressed protein intake, mTORC1 signaling, and leucine threshold failure

At the intracellular level, MyoPS is gated principally through the insulin/IGF-1–PI3K–Akt–mTORC1 axis. Ligand binding activates insulin receptor substrate-1, which recruits phosphoinositide 3-kinase (PI3K) and downstream Akt (protein kinase B); phosphorylated

Akt activates the mechanistic target of rapamycin complex 1 (mTORC1), which drives translation initiation via p70S6 kinase and 4E-BP1, while simultaneously phosphorylating Forkhead box O (FoxO) transcription factors to sequester them in the cytoplasm and suppress their transcription of atrophy-related genes (Seliem & Ragab, 2026). Dietary protein — and leucine specifically — is not merely a substrate for this process but an independent trigger of it: mTORC1 activation in skeletal muscle shows an approximately threshold-dependent response to leucine availability per feeding occasion, below which translation initiation is only weakly stimulated regardless of total daily protein intake (Cannavaro et al., 2025).

This creates a specific vulnerability in GLP-1 RA-treated patients. Profound appetite suppression does not merely lower total daily protein intake below the 1.2–1.6 g/kg/day target discussed in Section 6; it plausibly reduces the size of individual eating occasions below the per-meal leucine threshold required to trigger mTORC1 activation at all, converting what might appear as a modest total shortfall into a series of meals that fail to stimulate MyoPS in any meaningful way. Adding further complexity, GLP-1 receptor agonism recruits skeletal muscle microvasculature, increasing capillary surface area and the interstitial delivery of insulin, glucose, and amino acids to myocytes (Katsanos et al., 2026). In principle this vascular effect is pro-anabolic. In practice, its benefit is conditional on adequate circulating amino acids being available to deliver — a condition that severe appetite suppression may not satisfy. The same drug class may therefore be simultaneously improving the delivery infrastructure for anabolism while removing the substrate that infrastructure exists to transport, a tension explored further in Section 2.4.

2.3. Reduced NEAT, mechanical unloading, and atrophy-signaling pathways

Muscle protein breakdown during GLP-1 RA therapy is not solely a passive consequence of reduced synthesis; it is actively driven through the ubiquitin-proteasome system (UPS), the dominant proteolytic pathway in skeletal muscle wasting. De-repressed FoxO, released from Akt's inhibitory control under low insulin/IGF-1 signaling, upregulates the muscle-specific E3 ubiquitin ligases MuRF1 (TRIM63) and MAFbx/Atrogin-1, which tag myofibrillar proteins for degradation by the 26S proteasome; nuclear factor kappa B (NF-κB) signaling, triggered by adipose-derived pro-inflammatory cytokines, reinforces this same ligase upregulation through a parallel route (Seliem & Ragab, 2026). Superimposed on this intracellular signaling is the myostatin–activin–Smad2/3 axis: myostatin and activin A act via the activin type II receptor (ActRII) to phosphorylate Smad2/3, which both suppresses myogenic regulatory factors and cooperates with FoxO to activate the same atrogene program.

This is not merely a mechanistic aside — pharmacological antibody blockade of ActRII in obese mice preserves skeletal muscle mass and enhances fat loss during concurrent GLP-1 RA administration, providing direct, if preclinical, evidence that this axis is mechanistically active in the GLP-1 RA weight-loss context specifically, and that it is a tractable pharmacological target independent of the GLP-1 pathway itself (Nunn et al., 2024).

The observed reduction in daily step counts and moderate-to-vigorous physical activity following GLP-1 RA initiation (Maharjan et al., 2026) supplies a plausible mechanical trigger for this same signaling cascade. Reduced habitual loading is a well-established, independent activator of FoxO-mediated atrogene transcription, distinct from and additive to any purely energy-deficit-driven effect. Whether the resulting pattern more closely resembles classic disuse atrophy — reversible, dominated by reduced synthesis, without a strong inflammatory or proteolytic signature — or the disease-induced, cachexia-like atrophy seen in some inflammatory and malignant conditions, dominated by UPS-driven proteolysis and comparatively resistant to simple reloading, is not yet established for GLP-1 RA-treated patients specifically (Malavaki et al., 2015). The distinction matters clinically because the two patterns respond differently to resistance training, and it is flagged as an open question in Section 8.

2.4. Integration, an unresolved paradox, and a preclinical caveat

Bringing together the preceding sections yields the conceptual model adopted here: negative energy balance lowers the substrate and hormonal drive for MyoPS; suppressed protein intake compounds this by failing to reach the per-meal threshold required for mTORC1 activation; and reduced mechanical loading independently drives FoxO/UPS- and myostatin/Smad-mediated proteolysis. Together, these three inputs are proposed to produce a state of anabolic resistance analogous to that described in aging and critical illness, but occurring here as a side effect of otherwise highly effective pharmacotherapy in a population with no independent reason to be anabolically resistant.

This model sits uneasily alongside a genuine paradox in the preclinical literature. GLP-1 receptor activation, at the cellular level, is generally reported to activate the AMPK–SIRT1–PGC-1α axis and suppress NF-κB signaling — effects that, taken in isolation, should be protective against the very atrophy program described above, not permissive of it (Seliem & Ragab, 2026). If GLP-1 signaling is intrinsically anti-catabolic, the pooled fat-free-mass loss documented in Section 1, and the higher figures reported in some individual cohorts, cannot

be straightforwardly attributed to a direct catabolic action of the drug on muscle. The more parsimonious resolution is that the muscle loss observed in clinical practice is predominantly a downstream consequence of the rate and magnitude of weight loss and the accompanying reduction in mechanical loading, rather than direct pharmacological toxicity to myocytes; this is consistent with the observation in Section 2.1 that lean-mass loss tracks deficit size across weight-loss modalities generally, not only under GLP-1 RA therapy.

A more recent preclinical finding complicates this resolution. In diet-induced obese mice, semaglutide reduced skeletal muscle mass while preserving contractile force under steady-state conditions — a pattern broadly consistent with the energy-deficit account — but selectively impaired muscle regeneration after injury, producing smaller regenerated myofibers via a mechanism traced to reduced prostaglandin E2 (PGE2) signaling and consequently impaired muscle stem cell (satellite cell) proliferation; pharmacological restoration of PGE2 signaling fully rescued this regenerative deficit without compromising fat loss (Nalbandian et al., 2026). This finding is preclinical, semaglutide-specific, and its translation to human resistance-training-induced muscle damage is untested. It nonetheless raises a mechanistically distinct and practically important possibility: that GLP-1 RA therapy may not meaningfully impair muscle at rest, yet may specifically blunt the satellite-cell-dependent repair and remodeling process that resistance training relies upon to produce hypertrophic adaptation. If this proves translatable to humans, it would argue for training approaches that manage cumulative muscle damage and prioritize recovery capacity (Section 5.6) rather than approaches that maximize damage on the assumption that repair capacity is unaffected.

Finally, muscle mass loss under an effective weight-loss intervention does not, by itself, establish functional harm. In bariatric surgery, which produces substantially larger absolute lean-mass losses than any GLP-1 RA regimen, the net effect on muscle-to-fat ratio and measured muscle function is often favorable, such that the overall risk of clinically meaningful sarcopenic obesity may decrease despite the loss of muscle mass in absolute terms (Orioli et al., 2026). This does not imply that GLP-1 RA-associated muscle loss is unimportant — the exercise and nutritional barriers unique to this drug class, discussed in Section 4, are real and distinct from those facing bariatric surgery patients — but it does justify the pivot, taken up in Section 3, from raw muscle mass toward muscle quality and function as the clinically meaningful endpoint.

3. From Muscle Quantity to Muscle Quality

Sections 1 and 2 used “fat-free mass” and “lean mass” more or less interchangeably with “muscle,” following the convention of the trials and meta-analyses that report them. That convention warrants scrutiny. If DXA-derived fat-free mass is a biased and incomplete proxy for skeletal muscle, then the body-composition-paradox framing that motivates this review needs a more precise clinical endpoint before it can support a specific exercise prescription.

3.1. Limitations of DXA-derived fat-free mass as a proxy for skeletal muscle

Fat-free mass is not skeletal muscle. At the molecular level of the body-composition hierarchy, fat-free mass comprises total body water, protein, bone mineral, and soft-tissue minerals; skeletal muscle is only one tissue-level contributor to that total, alongside organs, connective tissue, and skin. Two distinct problems follow from collapsing this distinction, and both directly affect how the approximately 25% pooled fat-free-mass-loss figure should be read.

The first is a genuine measurement artifact. Adipose tissue itself is not pure fat: it carries an obligatory fat-free component — water, protein, and vasculature — that typically constitutes 15–20% of adipose tissue mass. When a patient loses fat mass under any intervention, some of that obligatory fat-free component is lost along with it, and DXA and similar methods register this as fat-free-mass loss even though no myofibril has been degraded (Tinsley & Heymsfield, 2024). At the weight losses now achieved with tirzepatide and semaglutide, this artifact alone can account for a non-trivial share of the reported lean-mass loss.

The second problem is that fat-free-mass hydration is not the constant that many body-composition equations assume. Classic work quantifying total body water relative to fat-free mass found a mean ratio of 0.719 in healthy volunteers versus 0.741 in protein-depleted surgical patients (Beddoe et al., 1985) — a small-looking difference that nonetheless invalidates any two-compartment model’s assumption of fixed fat-free-mass density and hydration in populations undergoing active tissue turnover, which by definition includes anyone in the midst of rapid, drug-induced weight loss. Empirically, in a longitudinal comparison of five body-composition methods (densitometry, deuterium dilution, DXA, MRI, and the four-compartment model) tracked over a mean follow-up of roughly three years, DXA showed considerable bias against the four-compartment reference standard, driven jointly by baseline fat percentage and by fat-free-mass hydration change; the authors concluded that only the four-compartment model and MRI can be used with confidence to assess body-composition change associated with weight change (Pourhassan et al., 2013). These limitations are compounded in the specific population of interest: bioelectrical impedance and

DXA both carry additional, well-documented sources of error at the higher body-mass-index range typical of GLP-1 RA candidates, including altered assumptions about torso thickness, hydration, and beam attenuation (Deurenberg, 1996; Johnson Stoklossa et al., 2016).

None of this discredits the body-composition-paradox literature — the approximately 25% pooled estimate remains the best available summary figure. It means the figure should be read as an approximate, method-dependent estimate of fat-free-mass change rather than a precise quantification of skeletal muscle loss, and that any clinical or research question turning on the difference requires a more specific endpoint than DXA-derived fat-free mass.

3.2. Muscle quality: neuromuscular function and intramuscular adipose tissue

If muscle mass is the wrong primary endpoint, muscle quality is the leading candidate to replace it — and the direct clinical evidence here is more encouraging than the alarm-oriented framing common in lay coverage of GLP-1 RA muscle loss would suggest. In a post-hoc MRI substudy of the SURPASS-3 trial, tirzepatide reduced thigh muscle volume roughly in proportion to overall weight loss but was also associated with a favorable reduction in muscle fat infiltration — a direct measure of myosteatosis — leading to the conclusion that the drug was associated with a potentially favorable change in muscle composition even as raw volume fell (Sattar et al., 2025). This is not an isolated finding: a broader synthesis of the lean-mass literature concludes that, in aggregate, GLP-1 RA therapy is associated with an improvement in muscle quality even as muscle quantity modestly decreases, while cautioning that this favorable pattern is unlikely to hold uniformly across all patients, and singling out those with chronic kidney disease (CKD), heart failure with reduced ejection fraction (HFrEF), or pre-existing frailty as subgroups where the balance of muscle loss to fat loss is less well characterized and plausibly less favorable (Neeland et al., 2024).

Human clinical function data point in the same direction, with an important caveat about who is being measured. In the SEMALEAN study, 106 adults with obesity completed 12 months of semaglutide 2.4 mg with DXA, handgrip strength, and resting energy expenditure assessed longitudinally; the study reported preserved lean mass and improved muscle function alongside substantial weight loss, though patients with a history of bariatric surgery showed the most pronounced reductions in body-composition parameters — an early signal that prior surgical weight loss, and by extension any pre-existing depletion of muscle reserve, may condition how favorably a given patient's muscle quality responds (Alissou et al., 2026). Consistent with this, independent longitudinal data on aging populations — not GLP-1 RA-

specific, but directly relevant to older or lower-muscle-reserve patients — show that loss of muscle thickness with age outpaces loss of cross-sectional area, and that intramuscular fat increases with age largely independent of any change in body weight or subcutaneous fat (Vieira et al., 2025). Intermuscular adipose tissue (IMAT) is now recognized as a distinct, age- and inactivity-sensitive fat depot with its own association to physical function, separate from — and in older adults sometimes a stronger predictor of functional decline than — total or even subcutaneous adiposity (Waters, 2019).

Taken together, this literature suggests a favorable default trajectory for muscle quality under GLP-1 RA-driven weight loss in the general case, with the caveat that this default is unlikely to be evenly distributed. Patients with pre-existing low muscle reserve, prior surgical weight loss, CKD, HFrEF, or reduced habitual activity are the plausible exceptions, and are exactly the patients for whom the exercise framework in Section 5 is most clearly indicated rather than merely optional.

3.3. Candidate functional endpoints

If muscle quality, not quantity, is the more defensible construct, it needs measurable proxies that a clinician can use. The ESPEN–EASO consensus statement on sarcopenic obesity is explicit that the diagnosis rests on impaired muscle strength and physical performance, not on low muscle mass in isolation; mass is a supporting criterion, not the diagnostic anchor (Donini et al., 2022). Four measures recur across this literature as practical, low-cost proxies: handgrip strength, a validated proxy for whole-body strength; the Short Physical Performance Battery (SPPB), a composite of gait speed, balance, and repeated chair-stand time, with established impaired-function thresholds below a summary score of roughly 8 out of 12; gait speed alone, with values under approximately 0.8 m/s flagging functional impairment in geriatric practice; and the Timed Up and Go (TUG) test, with durations at or above roughly 13.5 seconds associated with elevated fall risk.

None of these four measures has yet been validated specifically as an outcome in a GLP-1 RA resistance-training trial, so their inclusion here is a recommendation for what the proposed framework should be evaluated against, rather than a synthesis of existing GLP-1 RA-specific functional-outcome evidence — a gap addressed in Section 8. Practically, however, these measures share a property that makes them a natural bridge to the rest of the framework: each is a compound measure of both muscle quality and neuromuscular coordination, and each is

directly and plausibly modifiable by resistance training, unlike DXA-derived fat-free mass, which responds to fat loss itself as much as to any training stimulus.

4. Unique Clinical Barriers to Standard Exercise Prescription

The mechanistic case in Section 2 and the muscle-quality reframing in Section 3 both establish why exercise matters in this population. Neither explains why a generic "do resistance training" recommendation so often fails to translate into practice for patients on GLP-1 RA therapy. This section addresses that gap, organized around four barriers that are either unique to this drug class or unusually severe within it.

4.1. Delayed gastric emptying and exercise tolerance

GLP-1 receptor agonism slows gastric emptying by pharmacological design; this is part of the same mechanism that produces satiety and, by extension, weight loss. The clinical significance of this effect is larger than is often appreciated outside gastroenterology and anaesthesia. Joint 2025 clinical practice recommendations from the Australian Diabetes Society, the Australian and New Zealand College of Anaesthetists, and allied gastroenterology and obesity-medicine bodies state that current evidence does not support using the absence of gastrointestinal symptoms to rule out clinically meaningful delayed gastric emptying in patients on GLP-1 RA or dual GLP-1/GIP RA therapy, nor is there an evidence-based cessation window that reliably guarantees gastric emptying has normalized before a procedure (Hocking et al., 2025). This guidance was written for peri-procedural sedation and aspiration risk, not exercise, but the underlying physiological claim generalizes: symptom awareness is not a reliable proxy for gastric motility status in this population.

A small pilot study using body surface gastric mapping supplies direct mechanistic support for this claim. Eight patients with overweight or obesity — screened specifically to be free of gastrointestinal symptoms at baseline — underwent gastric electrophysiological testing before and during semaglutide 1 mg therapy. Five of the eight (63%) developed spectral abnormalities on the drug, and two developed a low or undetectable Gastric Alimetry Rhythm Index, indicative of myoelectrical dysfunction and poor coordination of gastric slow waves, despite still lacking overt symptoms (Abraham et al., 2026). The sample is small and the finding preliminary, but it converges with the peri-procedural guidance on the same practical conclusion: a patient who reports feeling well cannot be assumed, on that basis alone, to have normal gastric motility.

This has direct implications for exercise prescription. Advice to avoid training on a full stomach, or to exercise when the patient feels ready, implicitly assumes patients can accurately sense their own gastric state — an assumption the evidence does not support in this population. It strengthens, rather than weakens, the case for the exercise-timing recommendation in Section 5.1: if gastric-emptying delay cannot be reliably self-assessed, a structured default (training later in the day, away from the immediate postprandial window when drug-related motility effects are most pronounced) is more defensible than a purely symptom-guided approach.

4.2. Chronic nausea and fatigue

Gastrointestinal adverse effects are not a minor footnote in GLP-1 RA therapy: a recent primary-care-oriented review estimates that 40% to 70% of patients experience symptoms including nausea, vomiting, diarrhea, constipation, delayed gastric emptying, or biliary complications over the course of treatment (Saha et al., 2025). Nausea specifically has long been recognized as the single most commonly reported adverse effect of GLP-1 analog therapy in both clinical populations and preclinical models (Skibicka, 2013).

The neurobiology of GLP-1-associated nausea offers a partial explanation for why fatigue and reduced spontaneous activity travel alongside it rather than existing as separate problems. GLP-1 receptors are expressed not only in the gut and hindbrain satiety circuits but throughout the mesolimbic reward system, and animal studies suggest that stimulation of these mesolimbic populations can suppress food-motivated behavior through pathways that are neuroanatomically separable from nausea-driving circuits (Skibicka, 2013). This is a double-edged finding. On one hand, it implies that some of the appetite-suppressing action of GLP-1 RAs is not mechanistically inseparable from nausea. On the other, the same body of preclinical work reports that peripheral GLP-1 receptor agonism can reduce spontaneous locomotor activity in some rodent studies, though this finding is inconsistent across studies and doses (Skibicka, 2013). Translated cautiously to humans, this offers a plausible central-nervous-system contribution to the observed decline in non-exercise activity, operating in parallel with purely behavioral explanations such as reduced caloric intake lowering the energy available for incidental movement. This connection is drawn from rodent data and is presented as a mechanistic hypothesis warranting direct testing in humans, not as an established human finding.

4.3. Appetite suppression and nutrient-timing constraints

Section 2.2 established the mechanistic case that appetite suppression can push individual meals below the leucine threshold required for meaningful mTORC1 activation. A clinical-management layer sits on top of that mechanism. First-line management of GLP-1 RA-associated gastrointestinal symptoms centers on dietary modification: smaller, more frequent meals; adequate hydration; and avoidance of high-fat or high-sugar foods, which are more likely to trigger symptoms given delayed gastric emptying (Saha et al., 2025). An international expert commentary synthesizing recommendations from the Diabetes and Nutrition Study Group similarly recommends a protein target above 1.2 g/kg/day, evenly distributed across meals and paired with both aerobic activity and structured resistance training, while explicitly naming gastrointestinal side effects as the leading cause of GLP-1 RA treatment discontinuation (Noronha et al., 2025). These two facts sit in tension: the nutritional strategy most likely to preserve muscle (frequent, protein-forward meals) is also the strategy most constrained by the symptom burden most likely to end treatment altogether. The nutritional hierarchy in Section 6 is built to manage that tension explicitly.

4.4. Adherence, behavioral, and psychological considerations

The final barrier is not physiological: generic exercise advice measurably fails to change outcomes in this population, while structured, supervised programming measurably succeeds. An expert roundtable convened specifically to address incretin-associated muscle loss concluded that supervised, structured exercise programs are more effective at limiting muscle loss during GLP-1 RA therapy than general advice or recommendations to exercise, with some evidence that behavior change initiated under supervision persists after the structured intervention ends (Mechanick et al., 2025). This is, in effect, direct empirical support for the premise of the present review: the knowledge gap identified in Section 1 — that "engage in resistance training" is necessary but clinically insufficient advice — is not merely a theoretical concern but a documented predictor of real-world failure. A comprehensive narrative review addressing the same problem independently argued for resistance exercise as an optimization strategy for body composition during incretin-based pharmacotherapy (Locatelli et al., 2024); the contribution of the present review is not to establish that resistance training matters here — that case is well made — but to specify, with explicit evidence tiers, what that training should look like given the barriers catalogued above.

Adherence to the medication itself is a related but distinct problem, since a patient who discontinues GLP-1 RA therapy altogether has a different clinical trajectory than one who continues therapy but skips exercise sessions. Beyond the gastrointestinal discontinuation driver already noted, route of administration is itself a barrier for some patients: a real-world retrospective study of oral semaglutide, adopted in part specifically to address injection aversion, reported that 82 of 93 enrolled adults (88%) remained in treatment at one year (Krajnc et al., 2025) — a completion rate that, while reassuring in absolute terms, still reflects a meaningful minority for whom therapy did not continue. Symptom unpredictability also carries a social and psychological dimension easy to overlook in a purely physiological framework: gastrointestinal side effects associated with this drug class are occasionally unusual and socially awkward, and the anticipation of an unpredictable symptom in a shared training environment is a plausible, if underexplored, deterrent to consistent attendance that sits alongside the purely physical barriers already discussed (Noronha et al., 2025).

An additional consideration connects these barriers directly to the training-loading strategy proposed in Section 5.2. A meta-analysis and meta-regression of resistance-training trials conducted under sustained energy deficit found that energy deficit selectively impairs lean-mass gains from resistance training while leaving strength gains comparatively intact, with a dose-response relationship: each additional 1000 kcal/day of deficit reduced the estimated effect size for lean-mass gain by roughly 0.31, with strength outcomes far less affected across the same range (Murphy & Koehler, 2022). This is not a GLP-1 RA-specific finding — the included trials used conventional caloric restriction — but it is directly applicable given the argument in Section 2.1 that GLP-1 RA-associated lean-mass loss is substantially a function of deficit magnitude. If an energy deficit of the size routinely produced by tirzepatide and semaglutide preferentially protects strength over hypertrophy as a training outcome, this is an independent line of evidence supporting an emphasis on higher-intensity, lower-volume resistance training in this population: not because hypertrophy is undesirable, but because it is the outcome least likely to be achievable under the conditions this population is actually training in, while strength — arguably the more function-relevant outcome — remains attainable.

5. Evidence-Informed Exercise Prescription Framework

Sections 2 through 4 established, in order, a mechanism, a target endpoint, and a set of barriers. This section converts those into an actionable prescription. Two features distinguish it from a conventional resistance-training guideline reproduced with a GLP-1 RA label

attached. First, every recommendation is explicitly tiered by evidence type. Second, the loading-strategy recommendation is derived from, and where necessary revised against, the most current sports-science literature rather than assumed.

5.1. Exercise timing

Shifting training toward afternoon or evening windows, away from the period of peak postprandial gastric-motility disturbance, is supported, though not proven, by the finding in Section 4.1 that symptom status cannot be relied upon to indicate gastric-emptying status in this population (Hocking et al., 2025; Abraham et al., 2026). Because patients cannot reliably self-assess when gastric motility has normalized on a given day, a structured default — training later in the day, and allowing a longer post-meal interval than would be prescribed in a non-pharmacologically appetite-suppressed population — functions as a precautionary heuristic rather than a symptom-contingent choice the patient can safely make in the moment. No trial has directly tested exercise timing against gastric outcomes or training adaptations in GLP-1 RA users; this recommendation is therefore an expert inference, labeled as such in Section 7.

5.2. Training loading strategy: intensity and proximity to failure

A defensible starting position is resistance training at moderate-to-heavy loads, on the logic that this population's tolerance for training duration is constrained (Section 4) and that hypertrophy — the outcome classically associated with heavy loading — is, per Section 2.1 and the energy-deficit dose-response relationship (Murphy & Koehler, 2022), the training outcome least attainable under sustained energy deficit. Recent sports-science literature both supports and substantially complicates this position, and warrants direct engagement.

The classical "repetition continuum," which assigns heavy loads to strength, moderate loads to hypertrophy, and light loads to endurance, does not hold up well under contemporary scrutiny. A systematic re-examination of the loading literature concludes that hypertrophy can be obtained, and in some cases optimized, across a wide spectrum of loading zones provided sets are taken sufficiently close to failure, undermining the assumption that heavy loading is a hypertrophy prerequisite (Schoenfeld et al., 2021). A subsequent dose-response meta-regression sharpens this: proximity to failure shows a clear, graded relationship with hypertrophy outcomes — training closer to failure produces more muscle growth in a dose-dependent fashion — but shows no comparably clear dose-response relationship with strength gains, meaning strength can be developed effectively without training to literal failure

(Robinson et al., 2024). A parallel randomized trial comparing single-set training performed to failure against single-set training left with two repetitions in reserve found that both approaches produced appreciable, broadly similar gains across muscle thickness, strength, power, and endurance over eight weeks (Hermann et al., 2025).

Taken together, these findings support a specific position. Load itself — whether a set is performed at 60% or 85% of one-repetition maximum (1RM) — is a less decisive variable than how close to failure the set is taken, and hypertrophy, not strength, is the outcome most sensitive to that variable. Because the arguments in Sections 2.1 and 3.3 already de-prioritize hypertrophy relative to strength and function as the more relevant and attainable goal in this population, the defensible synthesis is: moderate-to-heavy loads (a range rather than a fixed threshold), with sets terminated one to three repetitions short of failure rather than at literal failure. This remains consistent with the strength-oriented goal identified in Section 3.3 as the more defensible functional endpoint, and it avoids the disproportionate systemic fatigue cost of training to failure in a population already managing the compound fatigue burden described in Section 4.2, without meaningfully sacrificing the hypertrophy stimulus that non-failure training still provides. This synthesis is indirect evidence, extrapolated from a non-GLP-1 sports-science literature, and is labeled accordingly.

5.3. Progression across phases of weight loss

Because the energy-deficit dose-response relationship (Murphy & Koehler, 2022) implies that the size of the deficit at any given point in treatment — not merely its presence — modulates achievable hypertrophy, progression is best organized around the trajectory of the deficit rather than around fixed calendar time. Early in GLP-1 RA titration, before the full dose and full appetite-suppressive effect are established, the energy deficit is typically smaller and better tolerated; this is the most favorable window for familiarization and for building the technical competence needed to safely approach — without exceeding — proximity-to-failure targets later. As the dose titrates upward and the deficit deepens, expectations should shift explicitly toward maintenance of strength and neuromuscular function rather than continued hypertrophic progression. This progression scheme is an expert inference combining the energy-deficit dose-response data with standard periodization logic; it has not been tested as a protocol in GLP-1 RA users.

5.4. Concurrent aerobic exercise considerations

Resistance training is the central concern here, but it should not be prescribed to the exclusion of aerobic activity, both because aerobic activity carries independent cardiometabolic benefit and because the observed decline in non-exercise activity concerns spontaneous activity broadly, not resistance training specifically. The relevant question is whether combining the two modes undermines resistance-training adaptations through the interference effect long debated in exercise science. An updated systematic review and meta-analysis found that concurrent aerobic and strength training is broadly compatible with strength and muscle-size adaptations compared with strength training alone, though some interference can emerge at high aerobic training volumes or frequencies (Schumann et al., 2022). Applied to this population, this supports including moderate aerobic activity alongside the resistance-training framework, while cautioning against prescribing aerobic volumes high enough to independently compound the fatigue burden discussed in Section 4.2 — a caution that is itself an expert inference layered onto indirect evidence.

5.5. Population heterogeneity

The framework above is calibrated to a relatively young, otherwise metabolically uncomplicated patient with obesity. Section 3.2 identified older patients, those with prior bariatric surgery, and those with pre-existing low muscle reserve, CKD, or HFrEF as subgroups who may experience a less favorable balance of lean-mass loss to fat-mass loss and may tolerate aggressive proximity-to-failure training less well given compounded fatigue and slower recovery. For these patients, the framework's general shape — moderate-to-heavy loads, sets stopped short of failure, strength and function prioritized over hypertrophy — is expected to generalize, but the specific thresholds should be set more conservatively and progressed more slowly, with closer monitoring using the functional endpoints identified in Section 3.3. This is an expert inference; no GLP-1 RA-specific dose-finding data exist across these subgroups, and this absence is noted again in Section 8.

5.6. Recovery under compound stress: sleep, weekly volume tolerance, and autoregulation

The barriers catalogued in Section 4 — unpredictable gastrointestinal symptoms, fatigue with a plausible central-nervous-system component, and severe appetite suppression limiting recovery nutrition — mean that a fixed percentage-of-1RM prescription is a poor fit for how this population's capacity fluctuates day to day. Autoregulation offers a practical alternative.

The repetitions-in-reserve (RIR)-based rating of perceived exertion (RPE) scale, developed and validated specifically to let lifters estimate their proximity to failure during a set, gives patients and clinicians a shared, low-burden language for adjusting a session's actual difficulty to how the patient is tolerating training that day, without abandoning the proximity-to-failure targets specified in Section 5.2 (Zourdos et al., 2016). A subsequent comparison of percentage-based, RPE-based, RIR-based, and velocity-based training approaches found that these methods produce broadly comparable acute performance outputs but differ in their fatigue and soreness responses, suggesting the choice of autoregulation method is not neutral and should be selected with the specific burden of fatigue in mind (Cowley et al., 2025). For this population, an RIR-based approach is proposed as the most defensible default: it requires no equipment beyond patient self-report, directly encodes the proximity-to-failure logic established in Section 5.2, and allows a session to be scaled down on a high-symptom-burden day without requiring the patient to abandon the training plan altogether.

Two randomized controlled trials are, at the time of writing, actively testing structurally similar interventions: a four-arm trial randomizing adults initiating semaglutide or tirzepatide to control, resistance exercise, protein supplementation, or combined resistance exercise and protein, with quadriceps cross-sectional area as the primary outcome and strength and physical function as secondary outcomes (LEAN-PREP; NCT06885736); and a trial randomizing adults initiating tirzepatide to structured resistance exercise plus pharmacotherapy versus pharmacotherapy alone, using ultrasound-measured thigh muscle thickness and echo intensity as primary outcomes (NCT07609160). Neither has reported results, and neither tests the specific proximity-to-failure and autoregulation logic proposed here; both test resistance training as a general intervention. Their existence nonetheless confirms that the knowledge gap this review addresses is being actively investigated.

6. Nutritional Intake Hierarchy

Section 2.2 established the mechanistic case for why appetite suppression threatens muscle protein synthesis: individual meals may fall below the per-meal leucine threshold required to activate mTORC1, regardless of total daily intake. Section 4.3 established the clinical-management layer: dietary modification is already the first-line response to GLP-1 RA gastrointestinal symptoms. This section turns those observations into a practical, tiered nutritional hierarchy, explicit throughout about how much of that hierarchy rests on direct evidence versus extrapolation.

6.1. The target intake and the evidence surrounding it

The starting point of 1.2–1.6 g/kg/day of protein is standard sports-nutrition and clinical guidance for preserving lean mass during any weight-loss intervention. What is specific to the GLP-1 RA context is a methodological difficulty in the underlying evidence base. A systematic review examining how randomized controlled trials of liraglutide, semaglutide, and tirzepatide report dietary intake and quality found that, of the trials collecting dietary data at all, only a minority reported outcomes, and most relied on single-timepoint assessments (such as ad libitum test meals) that likely underestimate real-world nutritional patterns and cannot be extrapolated to habitual intake over months of therapy (Jansson et al., 2026). An independent scoping review reached the same conclusion via a different search strategy: of 129 trials of these drugs, only 36 collected dietary data and just 10 reported outcomes from it (Babazadeh et al., 2025). The pivotal trials that established the efficacy of these drugs were, for the most part, not designed to characterize what happens to a patient's diet over months of profound appetite suppression. The 1.2–1.6 g/kg/day target is therefore retained as the correct clinical goal on physiological grounds, but the claim that it is routinely unmet in this population is treated here as a plausible inference from the leucine-threshold mechanism (Section 2.2) and the symptom burden (Section 4), rather than as a directly evidenced finding — a distinction reflected in the evidence tier assigned in Section 7.

6.2. A practical hierarchy: post-exercise prioritization, liquid formulations, leucine-rich distribution

Given that the full target is often unreachable, the practical question is where to spend a limited protein budget for maximum anabolic return. The strongest available evidence, though not drawn from a GLP-1 RA population, supports prioritizing the post-exercise window. In a controlled feeding study, three days of caloric restriction blunted the anabolic hormonal response to resistance exercise relative to energy balance, and this blunting occurred regardless of whether the post-exercise meal contained carbohydrate or protein, though protein provision still outperformed carbohydrate alone on downstream anabolic markers (Murphy & Koehler, 2020). This is a direct experimental demonstration of the anabolic-resistance construct central to Section 2 — energy deficit measurably blunts the body's response to a training stimulus — and it argues for concentrating available protein intake around training sessions specifically, when the anabolic stimulus from exercise is at least partially offsetting the deficit-driven blunting, rather than spreading a shortfall evenly across a day with no clear peak. This does not license abandoning meal regularity altogether: a short-

term feeding trial found that intermittent fasting and continuous energy restriction over ten days did not measurably impair integrated rates of muscle protein synthesis relative to a regular-meal control diet, suggesting that irregular meal timing per se is not the primary threat to MyoPS that the leucine-threshold argument might imply in isolation (Kouw et al., 2024). Taken together, these findings suggest the hierarchy should prioritize what and how much protein is delivered around training, more than enforcing a rigid schedule for the remainder of the day.

Below the post-exercise priority, liquid whey protein isolate is proposed as the next tier, both because it is calorically and volumetrically efficient relative to solid protein sources — a meaningful advantage when total food volume tolerance is reduced — and because of its gastric-emptying profile, discussed in Section 6.3. Below that, the hierarchy falls back to leucine-rich whole-food meals distributed across whatever eating occasions the patient can tolerate, prioritizing leucine density per meal (consistent with the threshold argument in Section 2.2) over strict adherence to a fixed number of meals per day.

6.3. Liquid protein under gastroparesis-like symptoms

The rationale for prioritizing liquid formulations is not purely theoretical. A study directly comparing liquid and solid test meals in patients with gastroparesis and functional dyspepsia found that liquid meals produced a materially different symptom and gastric myoelectrical activity profile than solid meals of comparable composition (Koch et al., 2023). While this trial was conducted in patients with primary gastroparesis and functional dyspepsia rather than GLP-1 RA-induced delayed emptying, the pathophysiological overlap — delayed antral emptying, impaired accommodation, symptom generation with solid but not liquid boluses — is close enough that this evidence is treated as indirect but reasonably strong, rather than as a direct GLP-1 RA finding. It provides mechanistic depth beneath the practical recommendation in Section 4.3 to favor liquid protein sources under this drug class.

6.4. Creatine monohydrate as an adjunct

Creatine monohydrate has among the strongest efficacy evidence of any commonly used sports-nutrition supplement for augmenting resistance-training-induced lean-mass gains in the general population, with meta-analytic evidence supporting benefit across age groups when paired with resistance training (Delpino et al., 2022). No study has tested creatine supplementation specifically in GLP-1 RA users, so its inclusion here is a mechanistic and

extrapolated recommendation, not a direct finding. Two considerations specific to this population temper an otherwise straightforward recommendation. First, essentially all supporting evidence for creatine's lean-mass benefit comes from studies pairing it with resistance training rather than administering it in isolation — the same meta-analysis finding creatine ineffective for lean-mass gain when taken without a training stimulus (Delpino et al., 2022) — meaning its expected benefit is conditional on the exercise prescription in Section 5 actually being followed; it is an adjunct to training, not a substitute for it. Second, creatine monohydrate can produce mild gastrointestinal discomfort (bloating, cramping) in a meaningful minority of users, particularly at the loading doses (around 20 g/day) sometimes used to accelerate saturation; in a population already managing delayed gastric emptying and chronic low-grade nausea (Sections 4.1–4.2), this side-effect profile is a genuine tolerability concern, and argues for starting at a low maintenance dose (3–5 g/day) without a loading phase, accepting a slower time to muscle saturation in exchange for materially better gastrointestinal tolerability. This dosing adjustment is itself an expert inference.

A final caveat applies to the entire nutritional hierarchy, not just to creatine: how achievable any of it is may depend on which GLP-1 RA agent a patient is using. Preclinical evidence indicates that tirzepatide's added GIP receptor agonism has an antiemetic effect that partially offsets the nausea otherwise driven by GLP-1 receptor activation, such that tirzepatide produced significantly fewer malaise behaviors than an equipotent dose of semaglutide in rodent models despite comparable appetite suppression and weight loss (Borner et al., 2025). This finding is preclinical and has not been confirmed as a clinical difference in gastrointestinal tolerability between the two drugs in humans. If it translates, it would mean the entire nutritional hierarchy — and the exercise-timing precautions in Section 5.1 — may be easier to execute on tirzepatide than on semaglutide, independent of any difference in efficacy. This is flagged as a research priority in Section 8, and echoes the liraglutide-versus-tirzepatide/semaglutide heterogeneity raised in Section 1: the framework has so far been written as though "GLP-1 RA" were a single pharmacological entity, and the accumulating evidence suggests that simplification will not hold indefinitely.

7. Evidence Strength Summary

A defining feature of this framework is that each recommendation is labeled by the kind of evidence supporting it, so that a clinician or reviewer can see at a glance what a given recommendation rests on, what population that evidence came from, and what would need to be true for the recommendation to be wrong. The tiers are: [D] direct clinical evidence in

GLP-1 RA-treated populations; [I] indirect evidence extrapolated from adjacent (non-GLP-1) obesity, dieting, or exercise-physiology populations; [M] mechanistic or preclinical rationale; and [E] expert inference — a synthesis or extrapolation step connecting other tiers that has not itself been directly tested. Many recommendations carry more than one tag.

Tables 1 and 2 tabulate the actionable recommendations in Sections 5 and 6. Sections 1 through 4 are foundational and diagnostic rather than prescriptive, and their principal claims are summarized in the accompanying text rather than tabulated exhaustively.

Table 1. Evidence tiers for the exercise prescription framework (Section 5).

#	Recommendation	Tier	Key support	Caveat
R1	Shift resistance training toward afternoon/evening windows, away from peak postprandial gastric-motility disturbance	[E]	Built on R2	No trial has tested exercise timing against gastric or training outcomes in GLP-1 RA users
R2	Do not rely on the absence of symptoms to infer that gastric motility has normalized before training	[D]	Hocking et al., 2025; Abraham et al., 2026	Strongest-evidence claim in Section 5; underlies R1 but is not itself about exercise
R3	Reject the classical repetition continuum as a strict constraint on load selection	[I]	Schoenfeld et al., 2021	Not tested in caloric-deficit or GLP-1 RA context specifically
R4	Train sets 1–3 repetitions short of failure rather than to literal failure	[I][E]	Robinson et al., 2024; Hermann	Extension to this population's symptom burden (Section 4.2)

#	Recommendation	Tier	Key support	Caveat
			et al., 2025	is an added inference
R5	De-prioritize hypertrophy relative to strength/neuromuscular function as the primary training goal	[I][E]	Murphy & Koehler, 2022	Bridge from a non-GLP-1 dose-response finding to goal-setting in this population is inference
R6	Organize progression around the trajectory of the energy deficit, not fixed calendar time	[E]	Murphy & Koehler, 2022; periodization principles	Not tested as a protocol in GLP-1 RA users
R7	Include moderate concurrent aerobic activity; avoid volumes high enough to independently compound fatigue	[I][E]	Schumann et al., 2022	Fatigue-compounding caution specific to this population is an added inference
R8	Identify higher-risk subgroups (older age, prior bariatric surgery, CKD, HFrEF, frailty, low muscle reserve) for closer monitoring	[D]	Neeland et al., 2024; Alissou et al., 2026	Identifies who is higher-risk; does not itself specify how training should differ
R9	Use more conservative loading/progression thresholds for the higher-risk subgroups in R8	[E]	Built on R8	No GLP-1 RA-specific dose-finding data exist across these subgroups
R10	Use RIR-based autoregulation to scale training to daily symptom/fatigue burden	[I][E]	Zourdos et al., 2016; Cowley et al., 2025	RIR chosen over alternatives for this population's day-to-day variability; not tested here directly

Table 2. Evidence tiers for the nutritional intake hierarchy (Section 6).

#	Recommendation	Tier	Key support	Caveat
R11	Retain 1.2–1.6 g/kg/day protein as the clinical target	[D]	Noronha et al., 2025	Derivation of the range traces to general sports-nutrition literature, not GLP-1-specific dose-finding
R12	Treat the target as realistically difficult to reach, and design the hierarchy around that difficulty	[M][E]	Leucine-threshold mechanism (Section 2.2); symptom burden (Section 4); Jansson et al., 2026; Babazadeh et al., 2025	No direct observational evidence for routine under-target intake in this population was identified; the two evidence-gap reviews concern the trial record's silence, not patients' actual intake
R13	Prioritize protein intake around the post-exercise window when the full daily target cannot be met	[I][E]	Murphy & Koehler, 2020	Direct experimental demonstration, but not in a GLP-1 RA population
R14	Do not over-index on rigid meal timing; short-term irregular meal patterns do not appear to independently impair MyoPS	[I]	Kouw et al., 2024	Ten-day trial; longer-term and GLP-1 RA-specific data do not exist
R15	Prioritize liquid whey protein isolate as the second tier of the hierarchy, below post-exercise timing	[M][E]	Volumetric/caloric efficiency; gastric-emptying profile (R17)	Ranking is an expert-inference ordering judgment, not a tested sequence
R16	Fall back to leucine-dense whole-food meals distributed flexibly across tolerated eating occasions	[M]	Cannavaro et al., 2025	Applies the Section 2.2 mechanism; not itself tested as an intervention

#	Recommendation	Tier	Key support	Caveat
R17	Favor liquid over solid protein formulations under gastroparesis-like symptoms	[I]	Koch et al., 2023	Direct clinical trial, but in primary gastroparesis/functional dyspepsia patients, not GLP-1 RA patients
R18	Use creatine monohydrate as a conditional adjunct to (not substitute for) the exercise framework	[I]	Delpino et al., 2022	No study has tested creatine in GLP-1 RA users specifically
R19	Use low-dose creatine maintenance (3–5 g/day) without a loading phase	[E]	Built on R18; background gastrointestinal burden (Sections 4.1–4.2)	Dosing adjustment not tested in this population
R20	Recognize that achievability of the hierarchy may differ by agent, with tirzepatide plausibly more tolerable than semaglutide	[M]	Borner et al., 2025	Preclinical; unconfirmed in humans; not a basis for agent selection on its own

Across the twenty recommendations, three rest on direct evidence in GLP-1 or dual GIP/GLP-1 receptor agonist-treated populations (R2, R8, R11), nine draw on indirect evidence extrapolated from adjacent populations (R3, R4, R5, R7, R10, R13, R14, R17, R18), four rest on mechanistic or preclinical rationale (R12, R15, R16, R20), and eleven involve an explicit expert-inference step connecting other tiers (R1, R4, R5, R6, R7, R9, R10, R12, R13, R15, R19); several recommendations carry more than one tag. No recommendation rests on a randomized controlled trial that directly tested this framework's specific exercise or nutritional protocol in a GLP-1 RA population, because no such trial has yet been completed.

This distribution is the expected shape of a hypothesis-generating clinical framework built by synthesizing adjacent evidence rather than by summarizing an evidence base that does not yet

exist. The strongest single piece of ground is the finding that symptom status cannot be trusted to indicate gastric motility (R2), which functions as a load-bearing premise for both the exercise-timing and nutritional-form recommendations that follow. The recommendations built partly or wholly on indirect, mechanistic, or expert-inference grounds should be weighted accordingly: as the most clinically actionable synthesis currently available, not as an already-validated protocol.

8. Knowledge Gaps and Future Research Priorities

The gaps below are organized by priority. Each corresponds to a specific recommendation or open question raised earlier in the review.

8.1. Highest priority: testing the exercise and nutrition prescription

A head-to-head training-intensity/proximity-to-failure randomized controlled trial in a GLP-1 RA population is the single highest-priority gap. The synthesis in Section 5.2 is built entirely from non-GLP-1 sports-science literature (Schoenfeld et al., 2021; Robinson et al., 2024; Hermann et al., 2025). No trial has randomized GLP-1 RA users to different proximity-to-failure targets and compared strength, hypertrophy, and — critically — gastrointestinal-symptom burden and session-completion rates as co-primary outcomes. This last point matters specifically for this population: a protocol that produces marginally better hypertrophy at the cost of substantially worse adherence, given the fatigue and nausea burden of Section 4, would fail in practice even if it succeeded on paper. Such a trial would directly test recommendations R3 through R5 and could move them from indirect/expert-inference to direct evidence.

A liquid-versus-solid protein form comparison under GLP-1 RA-associated delayed gastric emptying is the second priority. The rationale in Section 6.3 rests on a trial conducted in patients with primary gastroparesis and functional dyspepsia (Koch et al., 2023), not GLP-1 RA-induced delayed emptying. A trial directly comparing liquid versus solid protein delivery in GLP-1 RA patients, measuring both gastrointestinal tolerability and downstream muscle protein synthesis or strength outcomes, would directly test R15 and R17 and is achievable with existing methodology.

Exercise timing (Section 5.1) has never been tested against any outcome in this population. A crossover or parallel-arm design comparing morning against afternoon/evening training, with

gastrointestinal symptom logs and session-completion rates as primary outcomes, would directly test R1.

Functional endpoints as primary trial outcomes require validation. Section 3.3 proposed SPPB, gait speed, TUG, and grip strength as the endpoints the framework should be judged against, none of which has yet been validated as an outcome in a GLP-1 RA resistance-training trial. A pilot randomized controlled trial testing semaglutide against lifestyle counseling in older adults, using lean mass, 6-minute walk distance, grip strength, and SPPB as co-primary outcomes, is registered as completed (NCT05786521); a results publication was not identified at the time of writing. Notably, that trial does not include a resistance-training arm, so it will validate the endpoints without testing this framework's specific exercise prescription against them.

8.2. Drug-class and agent heterogeneity

The observation that liraglutide preserves lean mass more effectively than tirzepatide or semaglutide — most plausibly because it produces a smaller and slower energy deficit rather than through any distinct pharmacological mechanism (Section 2.1) — has not been translated into agent-specific guidance. No study has directly tested whether the exercise and nutritional recommendations here should differ by agent, dose, or titration speed. A patient titrating slowly on a lower-potency agent may face a meaningfully different anabolic-resistance trajectory than one on maximal-dose tirzepatide.

A related question is whether tirzepatide's GIP-mediated antiemetic effect (Borner et al., 2025) translates into meaningfully better real-world gastrointestinal tolerability than semaglutide in humans, which would mean the entire framework is easier to execute on one agent than the other, independent of comparative weight-loss efficacy. This is a directly and retrospectively answerable question for any dataset with paired gastrointestinal-symptom and adherence data from head-to-head trials such as SURMOUNT-5.

8.3. Population subgroup dose-finding

Section 5.5 identified older age, prior bariatric surgery, CKD, HFrEF, and low baseline muscle reserve as subgroups likely to need more conservative training thresholds, while noting that no GLP-1 RA-specific dose-finding data exist to set those thresholds precisely. A 24-month retrospective cohort study of older adults with type 2 diabetes on semaglutide found that grip strength initially improved but then declined over follow-up in men, while following

a different trajectory in women (Ren et al., 2025). This finding is retrospective, observational, and drawn from a single cohort, and should not be treated as established, but it raises the possibility that the framework's monitoring cadence may need to differ by sex as well as by the risk factors already identified. This is added as an explicit subgroup question for future dose-finding work.

8.4. Mechanistic and translational gaps

The pattern of atrophy — disuse versus cachexia — remains unresolved. Section 2.3 raised the question of whether GLP-1 RA-associated muscle protein breakdown more closely resembles reversible disuse atrophy or the more UPS-proteolysis-dominant, reload-resistant pattern seen in some inflammatory and malignant conditions (Malavaki et al., 2015), a distinction that matters because the two patterns respond differently to resistance training. Resolving this would require muscle biopsy or advanced imaging studies comparing atrogene expression and inflammatory markers in GLP-1 RA users with and without a structured resistance-training intervention.

The human translation of impaired satellite-cell-dependent muscle regeneration is untested. The preclinical finding that semaglutide preserves resting contractile force but selectively impairs post-injury regeneration via reduced PGE2 signaling (Nalbandian et al., 2026) would, if it translates, have a direct implication for the training-damage management logic in Section 5.2. A study using post-exercise muscle biopsy or MRI-based markers of exercise-induced muscle damage and repair kinetics in GLP-1 RA users versus matched controls would be the direct test.

The central-nervous-system contribution to reduced spontaneous activity remains speculative. The possibility that GLP-1 receptor agonism's mesolimbic and hypothalamic actions (Skibicka, 2013) contribute a central mechanism to the observed decline in non-exercise activity, independent of reduced caloric intake, is rodent-derived and untested in humans. Disentangling a central contribution from a purely energetic one would likely require doubly-labeled-water or accelerometry studies paired with controlled feeding, isolating activity change at matched caloric intake.

8.5. Nutritional and pharmacological-adjunct gaps

Creatine monohydrate has not been tested in GLP-1 RA users. Section 6.4 proposed creatine as a conditional adjunct with a tolerability-motivated dosing adjustment. A dose-finding or tolerability-focused randomized controlled trial, with gastrointestinal symptom

burden as a co-primary outcome alongside lean-mass and strength measures, would directly test R18 and R19 and could resolve whether the loading-phase avoidance recommended here is necessary or overly conservative.

Rigorous, longitudinal dietary-intake reporting should be embedded in future trials. Two independent reviews found that the pivotal RCTs establishing these drugs' efficacy rarely collected dietary-quality data and even more rarely reported it (Jansson et al., 2026; Babazadeh et al., 2025). This is a methodological gap, but arguably the most consequential one raised here, because every future trial testing the nutritional recommendations will need to build dietary-quality assessment in from the start rather than retrofitting it.

The muscle-preserving antibody landscape is developing rapidly, with implications for this framework's scope rather than its validity. Two combination-pharmacotherapy trials have reported human data extending the ActRII/myostatin-activin mechanism discussed in Section 2.3, where antibody blockade of this pathway preserved muscle and enhanced fat loss in mice (Nunn et al., 2024). In the phase 2b BELIEVE trial, bimagrumab (an anti-activin type II receptor antibody) combined with semaglutide limited lean-mass loss to a small fraction of what semaglutide alone produced, and bimagrumab monotherapy was associated with a lean-mass gain alongside fat loss (Heymsfield et al., 2026). Interim results from the phase 2 COURAGE trial, combining semaglutide with the anti-myostatin antibody trevogrumab, with or without the anti-activin A antibody garetosmab, reported that roughly 35% of semaglutide-induced weight loss was lean mass when semaglutide was used alone, and that adding trevogrumab spared an estimated 50–80% of that lean-mass loss (Regeneron Pharmaceuticals, 2026).

These developments matter for two reasons. First, they represent a direct, if unplanned, human validation of the mechanistic pathway discussed in Section 2.3, and strengthen confidence that the myostatin-activin axis is a real and modifiable contributor to GLP-1 RA-associated lean-mass loss. Second, both agents remain investigational, are not approved, and — as monoclonal antibodies requiring intravenous or specialty administration — are likely to face significant cost and access barriers even after approval, in a way that resistance training and dietary protein do not. The exercise-and-nutrition framework proposed here is not competing with these agents for the same clinical role; it is likely to remain the only broadly accessible intervention for lean-mass preservation for the majority of GLP-1 RA users for years after any such antibody reaches market, if it does. Moreover, the argument in Section 3.3 that mass and function are dissociable endpoints applies here: an antibody that preserves

or increases muscle mass has not thereby been shown to preserve the neuromuscular coordination, strength, and functional capacity that only a trained stimulus reliably produces. Whether patients on combination antibody-plus-GLP-1-RA therapy still benefit from structured resistance training is itself an open and currently untested question, and a natural extension of the present framework once these therapies become more widely available.

8.6. Trials to watch

Table 3 consolidates the trials whose results would most directly bear on the claims made here.

Table 3. Ongoing and recently reported trials relevant to the framework.

Trial	Focus	Status	Relevance
BELIEVE (bimagrumab ± semaglutide)	Activin-pathway antibody + GLP-1 RA on body composition	Completed; published 2026	Section 2.3 mechanism (human translation); Section 8.5
COURAGE (trevogrumab/garetosmab + semaglutide)	Myostatin/activin-A antibody + GLP-1 RA on body composition	Ongoing; interim results reported	Section 2.3 mechanism (human translation); Section 8.5
NCT05786521	Semaglutide vs. lifestyle counseling on lean mass, SPPB, 6-min walk, grip strength in older adults	Registry status: completed; results not yet located	Section 3.3 functional endpoints (no resistance-training arm)
LEAN-PREP (NCT06885736)	Control / resistance exercise / protein / combined during semaglutide or tirzepatide	Recruiting	Section 5 general premise; not the specific loading/autoregulation logic
NCT07609160	Structured resistance exercise + tirzepatide vs.	Recruiting	Section 5 general premise

Trial	Focus	Status	Relevance
	tirzepatide alone		
NCT07091500	GLP-1 RA with vs. without supervised and home-based exercise training	Recruiting	Section 5 general premise; includes an exercise-training arm
NCT07272837 (GLIMMER)	MRI tracking of muscle and cardiac composition over 12 months on semaglutide	Not yet recruiting	Section 3.1–3.2 muscle-quality endpoints

None of these trials tests the specific proximity-to-failure, autoregulation, or nutritional-hierarchy logic proposed here in full; several test resistance training as a general intervention, which will validate or falsify the broad premise of Section 5 without validating or falsifying its specific recommendations.

8.7. Prioritization summary

Of the gaps above, the highest-value next study is the head-to-head training-intensity trial in Section 8.1: it directly tests the largest expert-inference load-bearing claim (R3–R5), uses trial infrastructure and outcome measures that already exist in sports science, and would be feasible at modest scale. The second priority is the liquid-versus-solid protein comparison, for the same reasons of feasibility and direct relevance to a currently indirect-tagged recommendation (R17). The muscle-preserving antibody trials will continue to test the mechanistic model in Section 2.3 regardless of intent, and a positive, eventually-approved result would not eliminate the need for this framework so much as change the population it serves.

9. Conclusions

GLP-1 receptor agonist therapy has outpaced the exercise and nutrition science meant to accompany it. This review has attempted to narrow that gap into something clinically actionable without overstating the strength of the underlying evidence.

Three steps did that narrowing. First, a conceptual model of anabolic resistance — built from negative energy balance, suppressed protein intake, and reduced mechanical loading — was proposed as a synthesis of adjacent evidence rather than an established GLP-1-specific

disease process, and was tested against preclinical findings that complicate it. Second, DXA-derived fat-free mass was shown to be a biased proxy for skeletal muscle, and muscle quality and function were repositioned as the more defensible endpoint, with the direct clinical evidence on quality proving more reassuring than the quantity literature alone would suggest. Third, an actionable prescription was built around the barriers unique to this drug class — delayed gastric emptying that patients cannot reliably self-assess, compound fatigue, and appetite suppression severe enough to make standard protein targets aspirational — with a loading strategy derived from, and where necessary revised against, current sports-science literature.

None of this amounts to a validated protocol, and the evidence-strength summary in Section 7 makes that explicit and countable: of twenty specific recommendations, three rest on direct evidence in GLP-1 RA-treated populations, and the rest lean, in varying combinations, on evidence extrapolated from adjacent fields, mechanistic reasoning, or expert inference. This is the accurate description of a hypothesis-generating clinical framework, and it is offered as more clinically useful than the alternative it was written to replace: a one-line recommendation to engage in resistance training that carries an unstated and untested confidence of its own.

For the clinician treating a patient on GLP-1 RA therapy, the practical claim is narrower and more defensible than either extreme: not that muscle loss on these drugs is a crisis requiring intervention in every patient, and not that relative preservation means it can be safely ignored, but that a small, real, unevenly distributed risk can plausibly be shifted in the patient's favor by a specific, barrier-adapted combination of resistance training and nutritional prioritization. Patients with lower baseline muscle reserve, older age, prior bariatric surgery, or other risk factors identified in Section 5.5 are those for whom that judgment tilts most clearly toward intervention; patients without those factors, and with the generally favorable muscle-quality trajectory described in Section 3.2, may need the framework less urgently than the body-composition-paradox framing in isolation would suggest.

The surrounding landscape is moving quickly: two antibody-based combination therapies now have human phase 2 data testing a mechanism previously confined to animal models, and at least three independent trials are testing structured exercise as an adjunct to GLP-1 RA pharmacotherapy. The role of this review is to provide a defensible, tiered starting point while that evidence matures, and to identify precisely which of its own claims should be revised

first once it does. Whether the framework holds up is, by design, an empirical question — and one this review has sought to leave easier to answer than it found it.

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References

Abraham, R., Foong, D., Piya, M., Grudzinskas, K., & Ho, V. (2026). Semaglutide induces changes in gastric electrical activity in patients with overweight and obesity: A pilot study. Journal of Neurogastroenterology and Motility, 32(2), 237–243. https://doi.org/10.5056/jnm25156

Alissou, M., Demangeat, T., Folope, V., et al. (2026). Impact of semaglutide on fat mass, lean mass and muscle function in patients with obesity: The SEMALEAN study. Diabetes, Obesity and Metabolism, 28(1), 112–121. https://doi.org/10.1111/dom.70141

Aronne, L. J., Horn, D. B., le Roux, C. W., Ho, W., Falcon, B. L., Gomez Valderas, E., Das, S., Lee, C. J., Glass, L. C., Senyucel, C., & Dunn, J. P.; SURMOUNT-5 Trial Investigators. (2025). Tirzepatide as compared with semaglutide for the treatment of obesity. New England Journal of Medicine, 393(1), 26–36. https://doi.org/10.1056/NEJMoa2416394

Babazadeh, D., Wyatt, S., & Steinberg, F. M. (2025). Examining the omission of dietary quality data in glucagon-like peptide 1 clinical trials: A scoping review. Advances in Nutrition, 16(10), 100491. https://doi.org/10.1016/j.advnut.2025.100491

Beddoe, A. H., Streat, S. J., & Hill, G. L. (1985). Hydration of fat-free body in protein-depleted patients. American Journal of Physiology, 249(2 Pt 1), E227–E233. https://doi.org/10.1152/ajpendo.1985.249.2.E227

Bhandarkar, A., Bhat, S., & Kapoor, N. (2025). Effect of GLP-1 receptor agonists on body composition. Current Opinion in Endocrinology, Diabetes and Obesity, 32(6), 279–285. https://doi.org/10.1097/MED.0000000000000934

Borner, T., Pataro, A. M., Doebley, S. A., et al. (2025). Hypophagia and body weight loss by tirzepatide are accompanied by fewer gastrointestinal adverse events compared to semaglutide in preclinical models. Science Advances, 11(25), eadu1589. https://doi.org/10.1126/sciadv.adu1589

Cannavaro, D., Leva, F., Caturano, A., Berra, C. C., Bonfrate, L., & Conte, C. (2025). Optimizing body composition during weight loss: The role of amino acid supplementation. Nutrients, 17(12), 2000. https://doi.org/10.3390/nu17122000

Cowley, N., Nicholson, V., Timmins, R., et al. (2025). The effects of percentage-based, rating of perceived exertion, repetitions in reserve, and velocity-based training on performance and fatigue responses. Journal of Strength and Conditioning Research, 39(4), e516–e529. https://doi.org/10.1519/JSC.0000000000005026

Delpino, F. M., Figueiredo, L. M., Forbes, S. C., Candow, D. G., & Santos, H. O. (2022). Influence of age, sex, and type of exercise on the efficacy of creatine supplementation on lean body mass: A systematic review and meta-analysis of randomized clinical trials. Nutrition, 103–104, 111791. https://doi.org/10.1016/j.nut.2022.111791

Deurenberg, P. (1996). Limitations of the bioelectrical impedance method for the assessment of body fat in severe obesity. American Journal of Clinical Nutrition, 64(3 Suppl), 449S–452S. https://doi.org/10.1093/ajcn/64.3.449S

Donini, L. M., Busetto, L., Bischoff, S. C., et al. (2022). Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. Obesity Facts, 15(3), 321–335. https://doi.org/10.1159/000521241

Hermann, T., Mohan, A. E., Enes, A., et al. (2025). Without fail: Muscular adaptations in single-set resistance training performed to failure or with repetitions in reserve. Medicine & Science in Sports & Exercise, 57(9), 2021–2031. https://doi.org/10.1249/MSS.0000000000003728

Heymsfield, S. B., Aronne, L. J., Montgomery, P., Klickstein, L. B., Coleman, L. A., Dole, K., Mindeholm, L., Spruill, S., Li, X., & Attie, K. M.; BELIEVE Trial Investigators. (2026). Bimagrumab plus semaglutide alone or in combination for the treatment of obesity: A randomized phase 2 trial. Nature Medicine, 32(3), 869–882. https://doi.org/10.1038/s41591-026-04204-0

Hocking, S. L., Scott, D. A., Remedios, M. L., Horowitz, M., et al. (2025). 2025 ADS/ANZCA/GESA/NACOS clinical practice recommendations on the peri-procedural use of GLP-1/GIP receptor agonists. Anaesthesia and Intensive Care, 53(5), 300–306. https://doi.org/10.1177/0310057X251355288

Jansson, A. K., Gómez-Martín, M., Hedin, L., Clarke, E. D., Cross, V., Stanford, J., Taylor, R. M., Bogl, L. H., De Vlieger, N., Koochek, A., Löf, M., Asher, R. C., Burrows, T., Bucher, T., Sullivan, C., Nowicka, P., & Collins, C. E. (2026). A systematic review identifying critical evidence gaps in reporting dietary change in randomized controlled trials prescribing liraglutide, semaglutide, or tirzepatide. Obesity Reviews. Advance online publication. https://doi.org/10.1111/obr.70077

Johnson Stoklossa, C. A., Forhan, M., Padwal, R. S., Gonzalez, M. C., et al. (2016). Practical considerations for body composition assessment of adults with class II/III obesity using bioelectrical impedance analysis or dual-energy X-ray absorptiometry.

Current Obesity Reports, 5(4), 389–396. https://doi.org/10.1007/s13679-016-0228-5

Karakasis, P., Patoulias, D., Fragakis, N., & Mantzoros, C. S. (2025). Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: Systematic review and network meta-analysis. Metabolism, 164, 156113. https://doi.org/10.1016/j.metabol.2024.156113

Katsanos, C. S., Liu, Z., & Atherton, P. J. (2026). Glucagon-like peptide-1 receptor agonism and muscle health: Vascular and myocellular effects on glucose and protein metabolism. Comprehensive Physiology, 16(2), e70126. https://doi.org/10.1002/cph4.70126

Koch, K. L., Van Natta, M., Parkman, H. P., et al. (2023). Effect of liquid and solid test meals on symptoms and gastric myoelectrical activity in patients with gastroparesis and functional dyspepsia. Neurogastroenterology & Motility, 35(2), e14376. https://doi.org/10.1111/nmo.14376

Kouw, I. W. K., Parr, E. B., Wheeler, M. J., Radford, B. E., Hall, R. C., Senden, J. M., Goessens, J. P. B., van Loon, L. J. C., & Hawley, J. A. (2024). Short-term intermittent fasting and energy restriction do not impair rates of muscle protein synthesis: A randomised, controlled dietary intervention. Clinical Nutrition, 43(11), 2536–2546. https://doi.org/10.1016/j.clnu.2024.09.034

Krajnc, M., Kuhar, N., & Koceva, A. (2025). Oral semaglutide for the treatment of obesity: A retrospective real-world study. Frontiers in Endocrinology, 16, 1593334. https://doi.org/10.3389/fendo.2025.1593334

Locatelli, J. C., Costa, J. G., Haynes, A., Naylor, L. H., Fegan, P. G., Yeap, B. B., & Green, D. J. (2024). Incretin-based weight loss pharmacotherapy: Can resistance exercise optimize changes in body composition? Diabetes Care, 47(10), 1718–1730. https://doi.org/10.2337/dci23-0100

Look, M., Dunn, J. P., Kushner, R. F., et al. (2025). Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. Diabetes, Obesity and Metabolism, 27(5), 2720–2729. https://doi.org/10.1111/dom.16275

Maharjan, S., Dangol, G., & Le, Q. (2026, June 13–16). Losing pounds, not gaining steps: The paradox of GLP-1 receptor agonist therapy [Conference abstract]. ENDO 2026, Annual Meeting of the Endocrine Society, Chicago, IL, United States.

Malavaki, C. J., Sakkas, G. K., Mitrou, G. I., et al. (2015). Skeletal muscle atrophy: Disease-induced mechanisms may mask disuse atrophy. Journal of Muscle Research and Cell Motility, 36(6), 405–421. https://doi.org/10.1007/s10974-015-9439-8

Mechanick, J. I., Butsch, W. S., Christensen, S. M., Hamdy, O., Li, Z., Prado, C. M., & Heymsfield, S. B. (2025). Strategies for minimizing muscle loss during use of incretin-mimetic drugs for treatment of obesity. Obesity Reviews, 26(1), e13841. https://doi.org/10.1111/obr.13841

Murphy, C., & Koehler, K. (2020). Caloric restriction induces anabolic resistance to resistance exercise. European Journal of Applied Physiology, 120(5), 1155–1164. https://doi.org/10.1007/s00421-020-04354-0

Murphy, C., & Koehler, K. (2022). Energy deficiency impairs resistance training gains in lean mass but not strength: A meta-analysis and meta-regression. Scandinavian Journal of Medicine & Science in Sports, 32(1), 125–137. https://doi.org/10.1111/sms.14075

Nalbandian, M., et al. (2026). 15-PGDH inhibition promotes muscle repair and strength recovery during GLP-1 receptor agonist–induced weight loss. Proceedings of the National Academy of Sciences, 123(23), e2606533123. https://doi.org/10.1073/pnas.2606533123

Neeland, I. J., Linge, J., & Birkenfeld, A. L. (2024). Changes in lean body mass with glucagon-like peptide-1-based therapies and mitigation strategies. Diabetes, Obesity and Metabolism, 26(Suppl. 4), 16–27. https://doi.org/10.1111/dom.15728

Noronha, J. C., Van Gaal, L. F., Neeland, I. J., et al. (2025). Optimizing GLP-1 therapies for obesity and diabetes management. Obesity Pillars, 16, 100222. https://doi.org/10.1016/j.obpill.2025.100222

Nunn, E., Jaiswal, N., Gavin, M., et al. (2024). Antibody blockade of activin type II receptors preserves skeletal muscle mass and enhances fat loss during GLP-1 receptor agonism. Molecular Metabolism, 80, 101880. https://doi.org/10.1016/j.molmet.2024.101880

Orioli, L., Thissen, J. P., & Loumaye, A. (2026). Changes in body composition, muscle function, and muscle insulin sensitivity induced by obesity and bariatric surgery. Clinical Nutrition, 56, 106547. https://doi.org/10.1016/j.clnu.2025.106547

Pourhassan, M., Schautz, B., Braun, W., Gluer, C. C., Bosy-Westphal, A., & Müller, M. J. (2013). Impact of body-composition methodology on the composition of weight

loss and weight gain. European Journal of Clinical Nutrition, 67(5), 446–454. https://doi.org/10.1038/ejcn.2013.35

Regeneron Pharmaceuticals. (2026). Interim results from ongoing phase 2 COURAGE trial confirm potential of trevogrumab-based combinations to preserve muscle during weight loss [Press release]. https://newsroom.regeneron.com/news-releases/news-release-details/interim-results-ongoing-phase-2-courage-trial-confirm-potential/

Ren, Q., Zhi, L., & Liu, H. (2025). Semaglutide therapy and accelerated sarcopenia in older adults with type 2 diabetes: A 24-month retrospective cohort study. Drug Design, Development and Therapy. Advance online publication. https://doi.org/10.2147/DDDT.S531778

Robinson, Z. P., Pelland, J. C., Remmert, J. F., Refalo, M. C., Jukic, I., Steele, J., & Zourdos, M. C. (2024). Exploring the dose-response relationship between estimated resistance training proximity to failure, strength gain, and muscle hypertrophy: A series of meta-regressions. Sports Medicine, 54(9), 2209–2231. https://doi.org/10.1007/s40279-024-02069-2

Saha, B., Kamalumpundi, V., & Codipilly, D. C. (2025). GLP-1 and GIP receptor agonists: Effects on the gastrointestinal tract and management strategies for primary care physicians. Mayo Clinic Proceedings. Advance online publication. https://doi.org/10.1016/j.mayocp.2025.09.017

Sattar, N., Neeland, I. J., Dahlqvist Leinhard, O., et al. (2025). Tirzepatide and muscle composition changes in people with type 2 diabetes (SURPASS-3 MRI substudy). Lancet Diabetes & Endocrinology, 13(6), 482–493. https://doi.org/10.1016/S2213-8587(25)00027-0

Schoenfeld, B. J., Grgic, J., Van Every, D. W., & Plotkin, D. L. (2021). Loading recommendations for muscle strength, hypertrophy, and local endurance: A re-examination of the repetition continuum. Sports, 9(2), 32. https://doi.org/10.3390/sports9020032

Schumann, M., Feuerbacher, J. F., Sünkeler, M., Freitag, N., Rønnestad, B. R., Doma, K., & Lundberg, T. R. (2022). Compatibility of concurrent aerobic and strength training for skeletal muscle size and function. Sports Medicine, 52(3), 601–612. https://doi.org/10.1007/s40279-021-01587-7

Seliem, M. A., & Ragab, M. A. (2026). Molecular and cellular mechanisms of muscle–adipose tissue crosstalk driving sarcopenic obesity. Nutrition & Metabolism, 23, 57. https://doi.org/10.1186/s12986-026-01123-2

Skibicka, K. P. (2013). The central GLP-1: Implications for food and drug reward. Frontiers in Neuroscience, 7, 181. https://doi.org/10.3389/fnins.2013.00181

Stefanakis, K., Kokkorakis, M., & Mantzoros, C. S. (2024). The impact of weight loss on fat-free mass, muscle, bone and hematopoiesis health. Metabolism, 161, 156057. https://doi.org/10.1016/j.metabol.2024.156057

Tieland, M., van Dronkelaar, C., & Boirie, Y. (2019). Sarcopenic obesity in the ICU. Current Opinion in Clinical Nutrition and Metabolic Care, 22(2), 162–166. https://doi.org/10.1097/MCO.0000000000000547

Tinsley, G. M., & Heymsfield, S. B. (2024). Fundamental body composition principles provide context for fat-free and skeletal muscle loss with GLP-1 RA treatments. Journal of the Endocrine Society, 8(11), bvae164. https://doi.org/10.1210/jendso/bvae164

Vieira, F. T., Cai, Y., Gonzalez, M. C., Goodpaster, B. H., Prado, C. M., & Haqq, A. M. (2025). Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Reviews in Endocrine and Metabolic Disorders. Advance online publication. https://doi.org/10.1007/s11154-025-09941-0

Waters, D. L. (2019). Intermuscular adipose tissue: A brief review of etiology, association with physical function and weight loss in older adults. Annals of Geriatric Medicine and Research, 23(1), 3–8. https://doi.org/10.4235/agmr.19.0001

Zourdos, M. C., Klemp, A., Dolan, C., et al. (2016). Novel resistance training-specific rating of perceived exertion scale measuring repetitions in reserve. Journal of Strength and Conditioning Research, 30(1), 267–275. https://doi.org/10.1519/JSC.0000000000001049