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Protecting Muscle, Bone and the Stem-Cell Niche During GLP-1-Based Weight Loss: A Translational Review of Sarcopenia Risk, Common Adverse Effects and the SHIELD Mitigation Framework

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ABSTRACT

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual incretin agonists produce weight losses of 15-22% in obesity trials, but part of the lost mass is lean tissue. Whether this loss is an adaptive reduction proportional to smaller body size or a pathway to later sarcopenia, particularly in older adults and in people who stop treatment and regain weight, is unresolved. Common adverse effects (gastrointestinal intolerance, gallbladder disease, bone loss, hair shedding, peri-procedural aspiration risk) compound the clinical problem.

Methods and Findings: We performed a structured narrative review of randomized trials, body-composition substudies, meta-analyses, regulatory assessments, consensus statements and experimental studies on muscle and mesenchymal stem cells, with bibliographic metadata verified against Crossref. In dual-energy X-ray absorptiometry substudies, lean mass accounted for about 25-40% of weight lost; magnetic resonance data suggest that muscle quality may improve as fat infiltration falls. Weight regain after withdrawal is substantial, and we describe, as an explicitly hypothetical model, how repeated fat-predominant regain could ratchet body composition toward sarcopenic obesity. Preclinical data indicate that GLP-1RAs suppress myostatin and atrophy pathways, support myogenic factors and modulate mesenchymal stem-cell survival and lineage choice, but human satellite-cell data are lacking. Resistance training, protein intakes of 1.2-1.6 g/kg/day and combined aerobic-resistance programs have the strongest support for preserving lean mass and function. Investigational myostatin/activin-pathway antibodies reduced the lean fraction of weight loss in phase 2 trials, but are not approved for this use.

Conclusions: Lean loss during incretin therapy is real but heterogeneous, and its functional meaning depends on baseline muscle reserve, age, treatment duration and weight-cycling. We propose SHIELD (Screen, High-quality protein, Integrated training, Evaluate function, Limit collateral harms, Durable maintenance), a conceptual, non-validated framework that shifts monitoring from body weight to muscle function. Prospective studies with functional end points, direct muscle-mass measures and stem-cell biomarkers are needed.

Keywords: GLP-1 receptor agonists; sarcopenia; sarcopenic obesity; satellite cells; mesenchymal stem cells; resistance training

Abbreviations: ALM, appendicular lean mass; BIA, bioelectrical impedance analysis; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; MRI, magnetic resonance imaging; MSC, mesenchymal stem/stromal cell; NAION, non-arteritic anterior ischemic optic neuropathy; RCT, randomized controlled trial..

INTRODUCTION

Incretin-based drugs have changed obesity medicine. In the STEP 1 trial, once-weekly semaglutide 2.4 mg reduced body weight by 14.9% at 68 weeks, compared with 2.4% with placebo [1]; in SURMOUNT-1, the dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide produced mean reductions of up to about 21% at 72 weeks [2]. These results bring weight loss within the range previously associated with bariatric surgery and are now reaching large, older and multimorbid populations.

The magnitude and speed of weight loss create a problem that body weight alone cannot detect. Any substantial energy deficit removes lean tissue as well as fat, and the clinical relevance of that loss has become a matter of debate [3,4].

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For a middle-aged adult with high muscle reserve, losing several kilograms of lean mass may be a proportional adaptation to a smaller body. For an older adult, a person with low baseline strength, or someone who later stops treatment and regains mainly fat, the same loss may represent the first step toward sarcopenia, that is, low muscle strength combined with low muscle quantity or quality [5], or toward sarcopenic obesity [6]. Concern has been expressed that fat-free mass measured by dual-energy X-ray absorptiometry (DXA) does not equal skeletal muscle mass, and that older adults may be the group in whom loss matters most [7].

This review has three aims. First, to summarize, with attention to effect sizes and measurement methods, what is known about lean, muscle and bone changes during GLP-1 receptor agonist (GLP-1RA) therapy, and about the most common non-muscle adverse effects. Second, to bring a stem-cell perspective to the problem, examining what experimental work suggests about satellite cells, myostatin signaling and mesenchymal stem/stromal cells (MSCs). Third, to translate the evidence into a practical, explicitly provisional framework for preventing and managing lean loss and other common adverse effects. Throughout, we distinguish biological plausibility, clinical signals and regulatory approval, because these are frequently conflated in this rapidly growing field.

METHODS

This is a structured narrative review, not a systematic review or meta-analysis, and no new patient data were collected. We searched PubMed, PubMed Central, publisher websites and regulatory agency websites up to October 2026 using combinations of the terms GLP-1 receptor agonist, semaglutide, liraglutide, tirzepatide, lean mass, fat-free mass, skeletal muscle, sarcopenia, sarcopenic obesity, bone mineral density, adverse events, gallbladder, pancreatitis, alopecia, weight regain, resistance training, protein, creatine, myostatin, activin, bimagrumab, apitegromab, enobosarm, satellite cell and mesenchymal stem cell.

We prioritized (i) randomized controlled trials (RCTs) and their prespecified body-composition substudies; (ii) systematic reviews and meta-analyses; (iii) regulatory assessments and multisociety guidance; and (iv) mechanistic studies in animal models and human cells relevant to muscle and stem-cell biology. Company press releases were included only when no peer-reviewed report was available and are labeled as such. Bibliographic details of all references were checked against Crossref records. Evidence was graded qualitatively as high (consistent RCT or meta-analytic data), moderate (single RCTs, substudies or large observational cohorts), low (small trials, pharmacovigilance or surrogate end points) or preclinical. The SHIELD framework and the weight-cycling scenario presented in this article are original syntheses by the author and have not been tested prospectively.

BODY COMPOSITION DURING INCRETIN THERAPY

How much of the weight lost is lean tissue?

Body-composition substudies give a consistent but heterogeneous picture (**Table 1; Figure 1**). In the STEP 1 DXA substudy, about 40% of the weight lost with semaglutide was lean soft tissue [1,8]. In the SURMOUNT-1 DXA substudy (n = 160), tirzepatide reduced total body weight by 21.3%, fat mass by 33.9% and lean mass by 10.9%, so that roughly three-quarters of the weight lost was fat and one quarter lean [9].

Table 1. Body-composition changes in key incretin trials.

Study	Population and duration	Method	Weight change	Lean change	Lean share of loss	Evidence
STEP 1 DXA substudy [1,8]	Adults with obesity, no diabetes; semaglutide 2.4 mg; 68 wk	DXA	-14.9% (whole trial) vs -2.4% placebo	Lean soft tissue reduced	About 40%	Moderate (substudy)
SURMOUNT-1 DXA [9]	Adults with obesity (n = 160); tirzepatide; 72 wk	DXA	-21.3%	-10.9% (fat -33.9%)	About 25%	Moderate (substudy)
Network meta-analysis [10]	22 RCTs, 2,258 participants	Mixed (mostly DXA)	Varies by agent	Varies by agent	About 25% (pooled)	High-moderate
SURPASS-3 MRI [11]	Type 2 diabetes; tirzepatide vs insulin degludec; 52 wk	MRI	Not shown here	Thigh muscle volume -0.64 L vs comparator; fat infiltration -0.36 pp	In line with weight lost	Moderate (post hoc)
BELIEVE [12]	Obesity (n = 507); semaglutide, bimagrumab or both; 72 wk	DXA	-15.7% sema; -22.1% combination	-7.4% sema; -2.9% combination	28.2% sema; 7.2% combination	Moderate (phase 2)
EMBRAZE [13]	Obesity (n = 102); tirzepatide +/- apitegromab; 24 wk	DXA	Similar between arms	1.9 kg less lean loss with apitegromab	30.2% vs 14.6%	Moderate (phase 2)

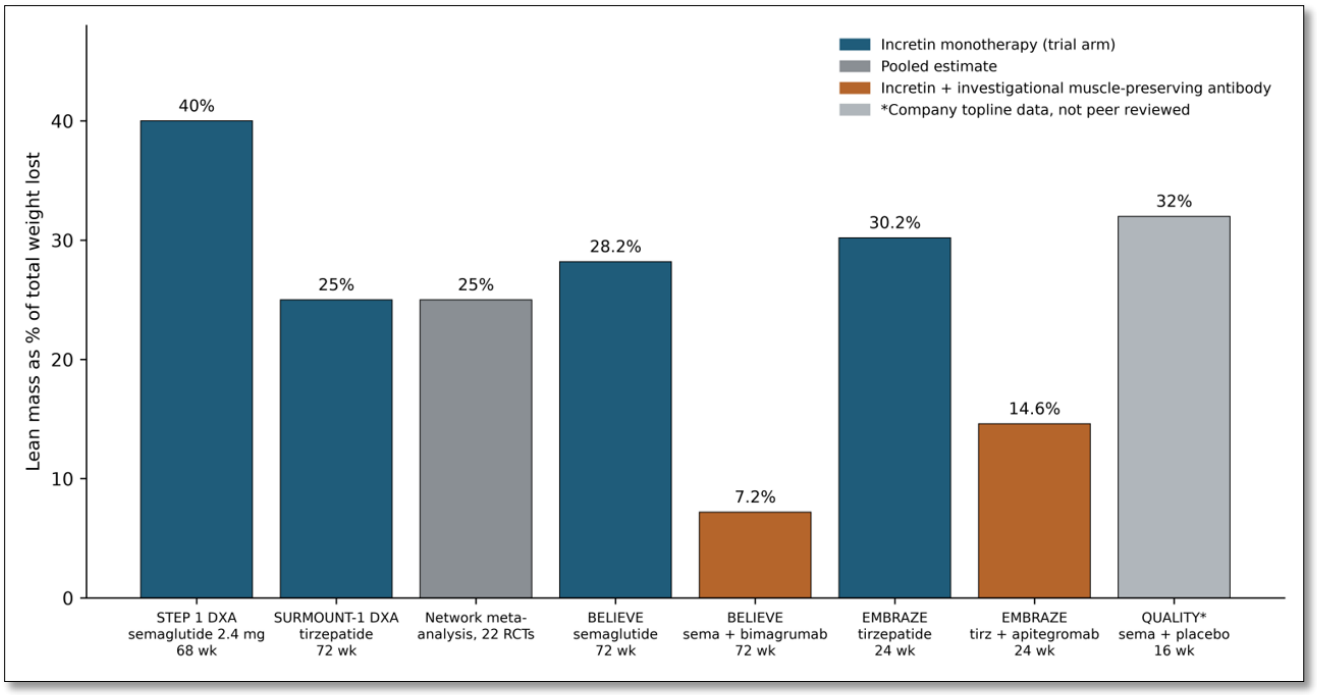


Figure 1. Lean mass as a share of total weight lost in incretin trials. Values are taken from the cited publications and differ in population, duration and measurement method (mostly DXA); they are not directly comparable. Sources, left to right: STEP 1 [1,8]; SURMOUNT-1 [9]; network meta-analysis [10]; BELIEVE [12]; EMBRAZE [13]; QUALITY [14]. QUALITY data are company topline results and have not been peer reviewed. Abbreviations: sema, semaglutide; tirz, tirzepatide; wk, weeks.

Reviews of incretin trials have reported lean fractions ranging from 15% or less to 40-60% of total weight loss, depending on the drug, the population and the method [8]. A network meta-analysis of 22 RCTs including 2,258 participants estimated that lean mass accounted for approximately 25% of weight loss with GLP-1RAs and co-agonists [10].

Two points qualify these figures. First, a lean fraction of 20-30% is broadly similar to that observed with caloric restriction and other forms of weight loss, which suggests that much of the effect is attributable to weight loss itself rather than to a direct catabolic action of the drugs [4,15]. Second, DXA lean soft tissue includes water, organs and connective tissue; it is not a direct measure of skeletal muscle, and short-term changes in hydration or glycogen can exaggerate apparent losses [3,7].

Muscle quantity versus muscle quality

Magnetic resonance imaging (MRI) adds information that DXA cannot. In a post-hoc analysis of the SURPASS-3 MRI substudy in type 2 diabetes, tirzepatide reduced thigh muscle volume by 0.64 L more than insulin degludec, but also reduced muscle fat infiltration by 0.36 percentage points, and the change in muscle volume was in the range expected for the degree of weight loss [11]. Linge, Birkenfeld and Neeland argued from such data that the muscle response to incretin therapy may be largely adaptive: muscle volume falls with lower body mass, while the composition of the remaining muscle improves [15].

The adaptive interpretation is reasonable for many participants in obesity trials, whose mean age is typically in the mid-forties and whose baseline muscle mass is often above average. It is less reassuring for older adults or for those already near diagnostic thresholds. The revised European definition of sarcopenia emphasizes strength (for example, grip strength below 27 kg in men or 16 kg in women, or five chair-stands taking longer than 15 s) as the primary criterion, with low appendicular lean mass (ALM) as confirmation [5]. The ESPEN/EASO consensus on sarcopenic obesity similarly requires impaired muscle function together with altered body composition, such as low ALM adjusted for weight [6]. None of the large incretin trials used these criteria as primary end points, and functional outcomes were rarely measured, which is the central evidence gap [3,7].

Lessons from weight loss in older adults

Lifestyle trials in older adults show both the risk and the remedy. In 160 dieting older adults with obesity, aerobic training alone was associated with the largest lean loss (about 2.7 kg), whereas resistance training alone (about 1.0 kg) or combined aerobic and resistance training (about 1.7 kg) attenuated the loss; the combined program produced the greatest improvement in physical function [16]. These data indicate that lean loss during intentional weight loss is modifiable and that the functional outcome depends more on the type of accompanying exercise than on the magnitude of weight loss alone.

Weight Regain and the Hypothesis of a Sarcopenic Ratchet

Incretin therapy is effective only while it is taken. In the STEP 1 extension, participants who stopped semaglutide regained about two-thirds of their prior weight loss within one year (11.6 of 17.3 percentage points), with a net reduction of 5.6% from baseline [17]. In SURMOUNT-4, participants who had lost 20.9% during a 36-week tirzepatide lead-in regained 14.0% after switching to placebo, whereas those who continued treatment lost a further 5.5% [18]. A systematic review of weight-management medications found that weight regain after cessation averaged about 0.4 kg per month, with return toward baseline within about 1.7 years [19].

The composition of regained weight has not been characterized in detail in incretin trials. If regain consists predominantly of fat, as has been suggested particularly for older adults [7], repeated cycles of treatment and withdrawal could progressively lower lean mass while restoring fat mass. **Figure 2** illustrates this concept with a deliberately simple, hypothetical scenario that is not based on patient data: assuming that 35% of a 15 kg loss is lean and that 15% of a 10 kg regain is lean, two cycles would leave a person 10 kg lighter than at baseline but with 7.5 kg less lean mass and a higher body-fat percentage (47.2% versus 45.0%). The input parameters are illustrative; the point is that a net reduction in body weight can coexist with a worse muscle-to-fat ratio. We term this possibility a sarcopenic ratchet and propose it as a testable hypothesis, not an established effect. It provides a rationale for including body-composition and functional measures during discontinuation and re-treatment, and for continuing exercise and adequate protein intake after the drug is stopped.

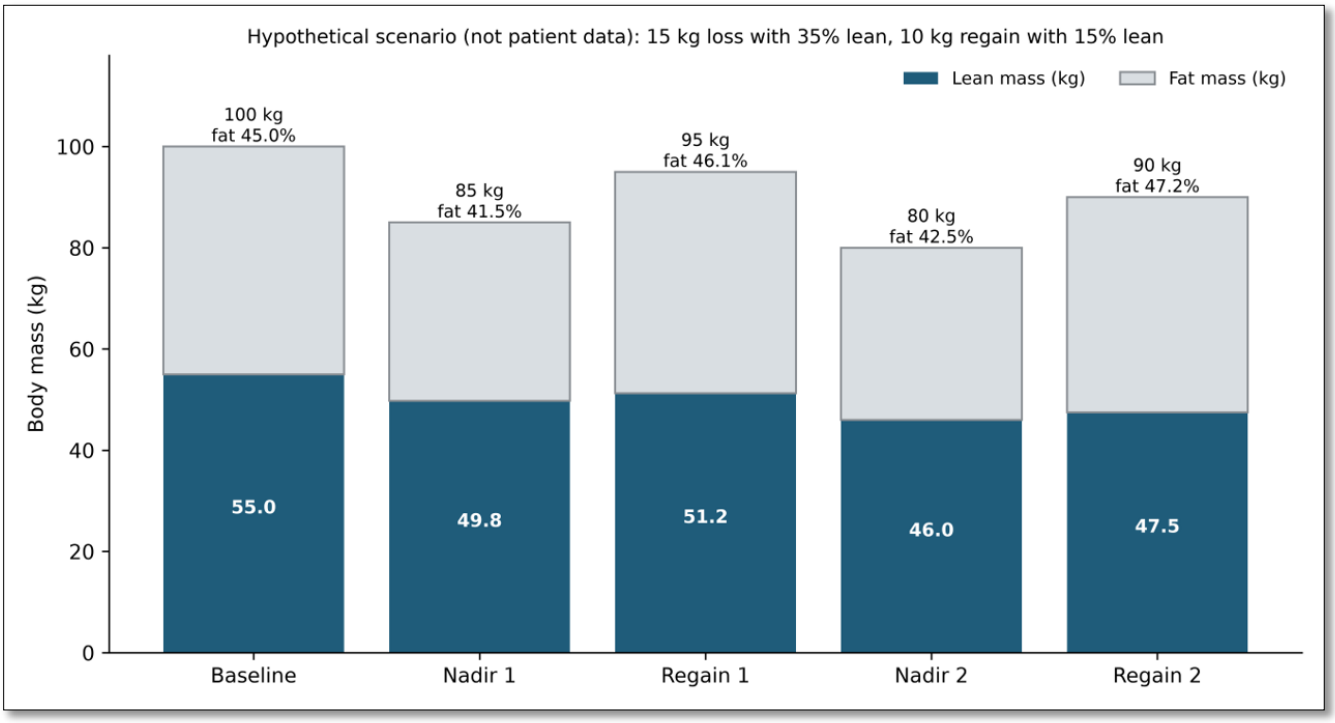


Figure 2. Hypothetical weight-cycling scenario illustrating the sarcopenic ratchet hypothesis. Not patient data. Assumptions: baseline 100 kg (45 kg fat, 55 kg lean); each loss of 15 kg is 35% lean; each regain of 10 kg is 15% lean. The model illustrates how lower body weight can coexist with a worse muscle-to-fat ratio.

A STEM-CELL PERSPECTIVE ON MUSCLE PRESERVATION

Satellite cells and the myostatin-activin axis

Skeletal muscle mass is regulated by the balance between protein synthesis and degradation in existing myofibers and, during regeneration and growth, by the activation of satellite cells, the resident muscle stem cells. Myostatin, a member of the transforming growth factor-beta family, restrains satellite-cell activation and self-renewal; in myostatin-null mice, satellite cells are more numerous and more readily activated [20]. However, hypertrophy driven by blockade of myostatin signaling can occur without satellite-cell contribution, indicating that the main effect on adult muscle mass is on the myofiber itself [21]. This distinction matters for interpreting both the risks of incretin-induced weight loss and the mechanism of investigational muscle-preserving antibodies, which act on myostatin, activin and their receptors (**Table 2**).

Experimental studies suggest that GLP-1RAs are not intrinsically catabolic in muscle. In mouse models of dexamethasone-induced and disease-related atrophy, exendin-4 reduced the expression of myostatin and of the

atrophy-related ubiquitin ligases atrogin-1 and MuRF-1, increased the myogenic factors MyoD and myogenin, and preserved muscle mass and function; dulaglutide had similar effects in dystrophic mdx mice [22]. Liraglutide attenuated skeletal muscle atrophy in rodent models [23], and liraglutide and semaglutide improved obesity-associated muscle atrophy through a sirtuin 1-dependent pathway [24]. A recent review summarizes additional effects on Akt/mTOR, AMPK-PGC-1alpha and mitochondrial biogenesis, while emphasizing that effects on human satellite cells have not been demonstrated [33]. These are preclinical findings in atrophy models, not in weight-reduced humans, and should not be read as evidence that GLP-1RAs build muscle in patients.

Table 2. Mechanistic and stem-cell evidence relevant to muscle preservation.

Topic	Model	Main finding	Level	Translational caveat
Myostatin and satellite cells [20]	Myostatin-null mice	Myostatin restrains satellite-cell activation and self-renewal	Preclinical	Mouse genetics; lifelong absence of myostatin
Hypertrophy without satellite cells [21]	Mice with myostatin blockade	Hypertrophy occurs mainly in existing myofibers	Preclinical	More lean mass does not equal more stem-cell capacity
GLP-1RAs in muscle atrophy [22-24]	Mouse atrophy and dystrophy models	Lower myostatin, atrogin-1, MuRF-1; higher MyoD, myogenin; SIRT1 involvement	Preclinical	Not tested in weight-reduced humans
GLP-1RAs and MSCs [25-29]	In vitro human and animal MSCs	Higher survival, proliferation, osteogenic and tenogenic differentiation; lower adipogenesis	Preclinical (systematic review)	Heterogeneous models; few in vivo data
Bone in patients [30,31]	RCTs in adults	Semaglutide or liraglutide alone lowered BMD; exercise preserved it	Moderate	Cell effects did not offset loading loss
Allogeneic MSCs in frailty [32]	Phase II RCT, n = 30 older adults	Better 6-minute walk distance and lower TNF-alpha with 100 million cells	Low (small RCT)	Not studied with GLP-1RA therapy

Mesenchymal stem cells, bone and adipose tissue

MSCs are the shared progenitors of osteoblasts, adipocytes, chondrocytes and tenocytes, and they also contribute to the fibro-adipogenic environment of muscle. A 2026 systematic review of 38 studies concluded that GLP-1RAs generally increase MSC proliferation, survival and osteogenic differentiation and reduce adipogenic differentiation in vitro, while noting heterogeneous models and few in vivo human data [25]. Exendin-4 promoted bone marrow MSC proliferation and migration and reduced apoptosis [26], protected MSCs against oxygen, glucose and serum deprivation through cAMP/PKA signaling and attenuation of endoplasmic reticulum stress [27], and induced tenogenic differentiation of human MSCs [28]. GLP-1 has also been proposed as a regulator of MSC behavior in the context of type 2 diabetes [29].

Clinical bone data do not yet confirm a protective net effect. In a 52-week RCT in 64 adults at increased fracture risk, semaglutide 1.0 mg increased the bone-resorption marker CTX and reduced areal bone mineral density (BMD) at the lumbar spine and total hip relative to placebo [30]. In a trial in adults with obesity after diet-induced weight loss, liraglutide alone reduced hip and spine BMD compared with exercise, whereas the combination of liraglutide and exercise preserved BMD [31]. Thus, the favorable in vitro profile of GLP-1RAs on MSC lineage choice appears to be outweighed in vivo by the skeletal consequences of weight loss and reduced mechanical loading, unless exercise is added.

A regenerative-medicine reader will also ask whether cell-based therapies could protect muscle during incretin therapy. The closest clinical evidence comes from aging frailty: in a phase II randomized, double-blind trial of 30 older adults, intravenous allogeneic bone marrow MSCs (100 million cells) improved 6-minute walk distance and reduced serum tumor necrosis factor-alpha at 6 months, without treatment-related serious adverse events [32]. No study has evaluated MSCs, MSC-derived extracellular vesicles or other cell products for preventing lean loss during GLP-1RA therapy, and such use should currently be confined to registered clinical trials.

Common Adverse Effects Beyond Muscle

Table 3 summarizes the most common and clinically relevant adverse effects, their approximate magnitude and practical mitigation. Gastrointestinal (GI) events are the most frequent. In STEP 1, 74.2% of semaglutide recipients and 47.9% of placebo recipients reported GI events, mostly nausea (44.2%), diarrhea (31.5%), vomiting (24.8%) and constipation

(23.4%); these were usually mild to moderate and transient, and led to discontinuation in 4.5% versus 0.8% [1]. Slow dose escalation, smaller and lower-fat meals, adequate hydration and pausing escalation when symptoms persist are the main countermeasures [34]. GI symptoms also reduce food intake and can make adequate protein intake more difficult, which links tolerability directly to muscle preservation.

Table 3. Common and notable adverse effects and practical mitigation.

Adverse effect	Approximate magnitude	Likely mechanism	Mitigation
Nausea, vomiting, diarrhea, constipation	GI events 74.2% vs 47.9% placebo; discontinuation 4.5% vs 0.8% (STEP 1) [1]	Delayed gastric emptying; central appetite effects	Slow titration; small, low-fat, protein-first meals; hydration; pause escalation [34]
Lean mass loss	About 25-40% of weight lost [8-10]	Energy deficit, unloading; possibly reduced intake of protein	Resistance plus aerobic training; protein 1.2-1.6 g/kg/day; monitor function [16,34]
Gallbladder and biliary disease	RR 1.37 overall; RR 2.29 in weight-loss trials [35]	Rapid weight loss; gallbladder motility	Avoid very rapid loss; evaluate right upper quadrant pain promptly
Pancreatitis	No robust increase in RCT meta-analyses [36]; labeled warning	Uncertain	Stop and evaluate if severe abdominal pain; caution with prior pancreatitis
Bone loss	Lower hip and spine BMD vs placebo or exercise [30,31]	Weight loss and reduced loading	Exercise; calcium and vitamin D; consider DXA in high-risk patients
Hair shedding	Modest pharmacovigilance signal [37]	Telogen effluvium from rapid weight loss	Adequate protein, iron and micronutrients; reassure that it is usually reversible
NAION	Very rare, up to 1 in 10,000 [38]	Uncertain	Urgent ophthalmic review for sudden visual loss
Peri-procedural aspiration	Case reports; guidance-based risk [39]	Residual gastric content	Individual risk assessment; 24-h liquid diet for high-risk; gastric ultrasound [39]
Weight regain after stopping	About two-thirds regained within 1 year [17,18]	Loss of drug effect on appetite	Plan long-term treatment or structured taper; maintain exercise [19,40]

Gallbladder and biliary disease are a consistent signal. A meta-analysis of 76 RCTs found an increased risk of gallbladder or biliary disease with GLP-1RAs (relative risk 1.37), higher in weight-loss trials (relative risk 2.29), at higher doses and with longer treatment, corresponding to about 27 additional events per 10,000 person-years [35]. Rapid weight loss is a known contributor. Pancreatitis remains a labeled warning, but meta-analyses of RCTs have not shown a statistically robust increase [36]. In a large observational analysis of United States veterans, GLP-1RA use was associated with lower risks of several neuropsychiatric, cardiometabolic and other outcomes, but with higher risks of GI disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis [41].

Rare but serious events deserve awareness. The European Medicines Agency concluded in 2025 that NAION is a very rare side effect of semaglutide (up to 1 in 10,000 users) [38]. Hair shedding, usually consistent with telogen effluvium related to rapid weight loss and nutritional stress, has been reported, and pharmacovigilance analyses suggest a modest disproportionality signal [37]. Delayed gastric emptying raises peri-procedural aspiration concerns; multisociety guidance in 2024 advised that most patients may continue GLP-1RAs before elective procedures, with a 24-hour liquid diet for those at higher risk and consideration of gastric ultrasound when residual gastric content is uncertain [39].

COUNTERMEASURES: WHAT WORKS AND HOW WELL

Nutrition

A joint advisory from four North American societies recommends protein intakes of about 1.2-1.6 g/kg of adjusted body weight per day (roughly 80-120 g/day for many patients), protein-first meal patterns, small frequent meals during periods of reduced appetite, and attention to micronutrients including vitamin D, calcium, iron and vitamin B12 [34]. The advisory also recommends resistance training and monitoring of nutritional status. In resistance-trained populations, the benefit of protein supplementation on lean mass plateaus at about 1.6 g/kg/day [42], suggesting that intakes above this level add little for most patients. Because GLP-1RAs reduce appetite and total intake, achieving these

targets often requires deliberate meal planning, a dietitian and, in some cases, protein supplements.

Exercise

Exercise is the intervention with the strongest evidence. In a randomized trial of weight-loss maintenance after a low-calorie diet, the combination of liraglutide and exercise produced the greatest reduction in body fat and best-preserved weight loss, compared with either intervention alone [40]. The same program preserved BMD, whereas liraglutide alone did not [31]. In older adults, combined aerobic and resistance training best protected function during weight loss [16]. Pragmatically, progressive resistance exercise two to three times per week for major muscle groups, combined with aerobic activity, should be started at or before treatment initiation, with supervision for older, frail or deconditioned patients.

Supplements

Creatine monohydrate combined with resistance training increased lean tissue mass by about 1.37 kg and improved strength in a meta-analysis of 22 RCTs in older adults [43]. It has not been tested specifically in GLP-1RA users, and creatine raises serum creatinine without changing kidney function, which should be considered when interpreting laboratory results. Vitamin D, calcium and vitamin B12 should be checked and corrected were deficient, in line with the joint advisory [34].

Investigational muscle-preserving drugs

Several drugs that target myostatin, activin or androgen receptors are being tested with incretins (**Table 4**). In an earlier phase 2 trial in adults with type 2 diabetes and obesity, the activin type II receptor antibody bimagrumab reduced fat mass by 20.5% while increasing lean mass by 3.6% over 48 weeks [44]. In the phase 2 BELIEVE trial (n = 507), bimagrumab plus semaglutide produced a 22.1% weight loss at 72 weeks versus 15.7% with semaglutide alone; 92.8% of the weight lost with the combination was fat, compared with 71.8% with semaglutide [12]. In the phase 2 EMBRAZE trial (n = 102), the myostatin-specific antibody apitegromab added to tirzepatide reduced lean mass loss by 1.9 kg over 24 weeks; lean mass made up 14.6% of total weight lost compared with 30.2% with tirzepatide alone [13]. In the phase 2b QUALITY trial in adults aged 60 years or older (n = 168), the selective androgen receptor modulator enobosarm added to semaglutide was reported to reduce lean-mass loss and declines in stair-climbing power; these data were released as company topline results and have not been published in a peer-reviewed journal [14].

Table 4. Investigational muscle-preserving agents combined with incretins.

Agent	Target	Trial	Main finding	Status for this use
Bimagrumab	Activin type II receptors	Phase 2 in T2D and obesity [44]; BELIEVE with semaglutide [12]	Fat loss with lean gain alone; 92.8% of loss as fat with combination	Investigational
Apitegromab	Latent and pro-myostatin	EMBRAZE with tirzepatide [13]	1.9 kg less lean loss; lean share 14.6% vs 30.2%	Investigational for obesity
Enobosarm	Selective androgen receptor modulator	QUALITY, adults >=60 y, with semaglutide [14]	Less lean loss and functional decline reported	Investigational; topline data only, not peer reviewed

These agents should be regarded as investigational for this indication. Larger and longer trials must establish whether preserving DXA lean mass translates into better strength, function, falls and fractures, and must define safety, including effects of activin blockade on other tissues [45]. None of these agents is approved for preserving muscle during GLP-1RA therapy.

The SHIELD Framework

To make the evidence usable in practice, we propose SHIELD, a six-step framework that reorients monitoring from body weight to muscle function (**Figure 3; Table 5**). S (Screen and stratify): before treatment, document grip strength, chair-stand time and gait speed, and, where available, body composition by DXA or validated bioelectrical impedance analysis (BIA); identify higher-risk patients, such as those aged 65 years or older, with frailty, low baseline strength, osteoporosis, previous weight cycling or very rapid expected weight loss. H (High-quality protein): set an individual protein target of 1.2-1.6 g/kg/day, distributed across meals, and correct micronutrient deficiencies. I (Integrated training): prescribe progressive resistance exercise combined with aerobic activity, supervised for higher-risk patients; creatine can be considered as an adjunct. E (Evaluate function): repeat the functional tests about every three months during active weight loss; a fall of more than 10% in grip strength, a new crossing of sarcopenia thresholds, or lean loss clearly above the expected 25-40% fraction should prompt slower dose escalation, a lower maintenance dose or a review of nutrition and exercise. L (Limit collateral harms): address GI tolerability, gallbladder symptoms, bone health, hair shedding, visual symptoms and peri-procedural planning. D (Durable maintenance): plan from the outset for long-term treatment or a structured taper, and maintain exercise and protein intake after discontinuation to reduce the risk of fat-predominant regain.

The thresholds in SHIELD are pragmatic choices derived from consensus definitions [5,6] and from the trial data summarized above; they have not been validated against clinical outcomes. SHIELD is intended as a structure for clinical care and for designing studies, not as a guideline.

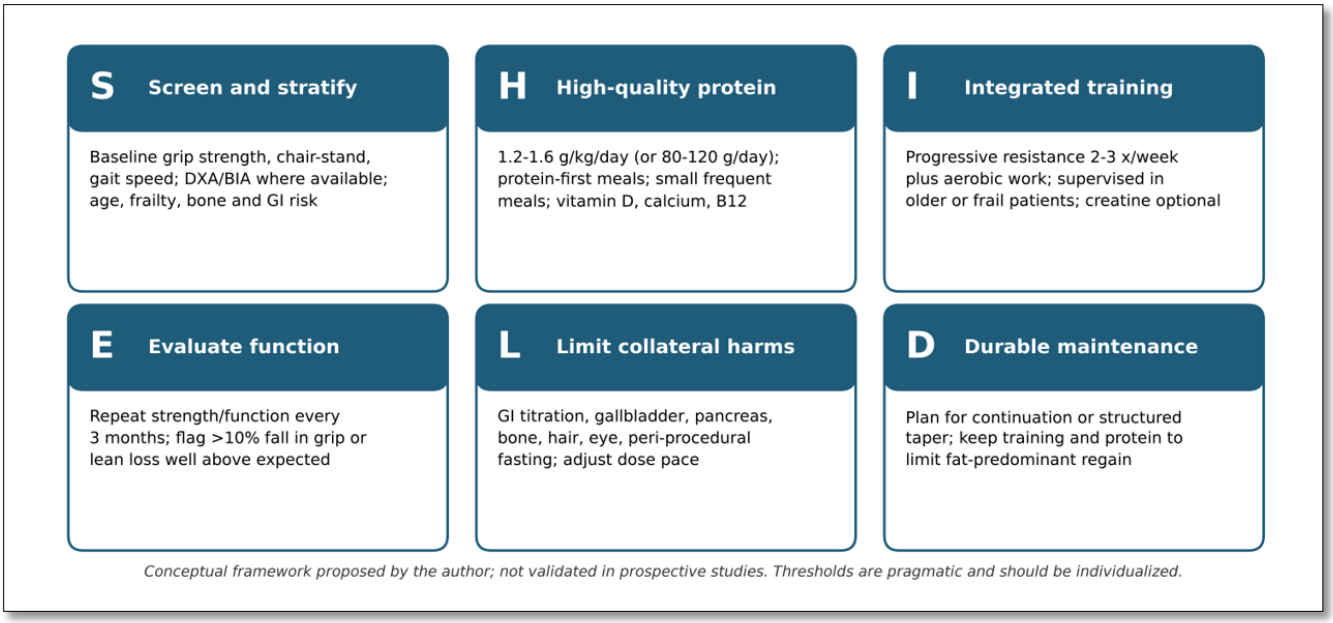


Figure 3. The SHIELD framework for muscle-focused care during GLP-1-based therapy. Conceptual framework proposed by the author. Thresholds are pragmatic, derived from consensus definitions and trial data, and have not been validated prospectively.

Table 5. The SHIELD framework: operational elements (conceptual, not validated).

Step	Core actions	Suggested measures and thresholds	Key supporting sources
S - Screen and stratify	Identify higher-risk patients before starting	Grip strength (<27 kg men, <16 kg women); 5 chair-stands >15 s; gait speed; DXA or BIA; age, frailty, osteoporosis, prior weight cycling	[5,6]
H - High-quality protein	Individual protein target; micronutrients	1.2-1.6 g/kg/day; protein at each meal; vitamin D, calcium, B12, iron	[34,42]
I - Integrated training	Resistance plus aerobic exercise	2-3 resistance sessions/week; supervision if older or frail; creatine optional	[16,40,43]
E - Evaluate function	Re-test during active weight loss	About every 3 months; act if grip falls >10%, sarcopenia thresholds are crossed, or lean share clearly exceeds 25-40%	[5,8-10]
L - Limit collateral harms	Anticipate common adverse effects	GI titration; gallbladder and pancreas symptoms; bone; hair; vision; peri-procedural plan	[1,30,31,35-39,41]
D - Durable maintenance	Plan beyond the weight-loss phase	Long-term treatment or structured taper; continue exercise and protein; re-assess body composition after stopping	[17-19,40]

DISCUSSION

The question of whether lean loss during incretin therapy is harmful cannot be answered with a single yes or no. The trial evidence supports three conclusions. First, lean tissue accounts for a meaningful but variable fraction of weight loss, typically about a quarter, with wide variation by drug, population and method [9,10]. Second, at least in some populations, muscle composition improves as fat infiltration

falls, which is consistent with an adaptive response [11,15]. Third, the people most likely to be harmed (older adults, people with low baseline muscle reserve, and people who cycle through treatment and withdrawal) are the least represented in trials and the least studied with functional outcomes [3,7].

The stem-cell perspective adds nuance. Preclinical studies suggest that GLP-1RAs suppress myostatin and atrophy pathways in muscle and favor osteogenic over adipogenic differentiation of MSCs [22,25]. If these effects occur in humans, part of the lean loss observed in trials would be driven by energy deficit and unloading rather than by the drug, which is consistent with the observation that exercise largely prevents it [16,31,40]. Conversely, the clinical bone data show that favorable cellular effects do not guarantee favorable tissue outcomes when mechanical loading falls [30]. The investigational antibodies make the myostatin-activin axis a direct therapeutic target, but the experimental evidence that myostatin blockade increases muscle mass mainly through myofiber hypertrophy rather than satellite-cell expansion [21] cautions against assuming that more lean mass will mean regenerative capacity or better function.

This review has limitations. It is narrative rather than systematic, and selection bias cannot be excluded. Many body-composition analyses are substudies with small samples and short follow-up, and they rely on DXA lean mass rather than direct skeletal muscle measures. Some evidence for investigational agents comes from company releases rather than peer-reviewed publications. The sarcopenic ratchet hypothesis and the SHIELD framework are original proposals that require empirical testing.

Research priorities follow directly. Trials should include strength and physical function as co-primary or key secondary end points; use direct muscle measures such as MRI or D3-creatine dilution in addition to DXA [7]; enroll older and frail participants; characterize the composition of regained weight after withdrawal; and test whether structured exercise and protein programs, or investigational muscle-preserving drugs, improve outcomes that matter to patients. Translational studies could measure satellite-cell number and function and MSC-related markers in muscle biopsies from treated patients, and any evaluation of cell-based approaches should take place within registered trials.

CONCLUSION

GLP-1-based therapies cause clinically important weight loss, of which roughly a quarter to two-fifths is lean tissue. For many patients this is a proportional and possibly adaptive change; for older, frail or weight-cycling patients it may accelerate sarcopenia. Common adverse effects, especially GI intolerance, gallbladder disease and bone loss, are frequent or consistent enough to require proactive management. The best-supported countermeasures are simple: resistance and combined exercise, adequate protein and micronutrients, careful dose titration and a long-term maintenance plan. Muscle-preserving drugs are promising but investigational, and stem-cell-based interventions are at an exploratory stage. The SHIELD framework offers a practical structure for shifting the clinical focus from how much weight is lost to how much muscle and function are preserved.

DECLARATIONS

Ethics approval and consent to participate: Not applicable. This review is based on published literature and public regulatory documents; no human participants, patient data or animals were involved.

Consent for publication: Not applicable.

Data availability: No new data were generated. The values shown in Figure 1 are taken from the cited publications; **Figure 2** shows a hypothetical calculation whose parameters are fully stated in the text and legend.

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