Incretin-based Therapy and muscle health

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Agenda

- Introduction
  - Incretin-based therapy- only benefits?
- Weight reduction and lean mass (muscle mass)
- How does it compare to other weight loss methods
- Why muscle mass is important?
- Muscle health and evaluation
- Muscle loss is adaptive or maladaptive?
- Muscle mass improvement
- Take home message

Benefits of incretin-based therapies:

- Weight loss
- Better Glycemic control
- Cardiovascular benefits
- Renal benefits
- MASLD
- Sleep apnea

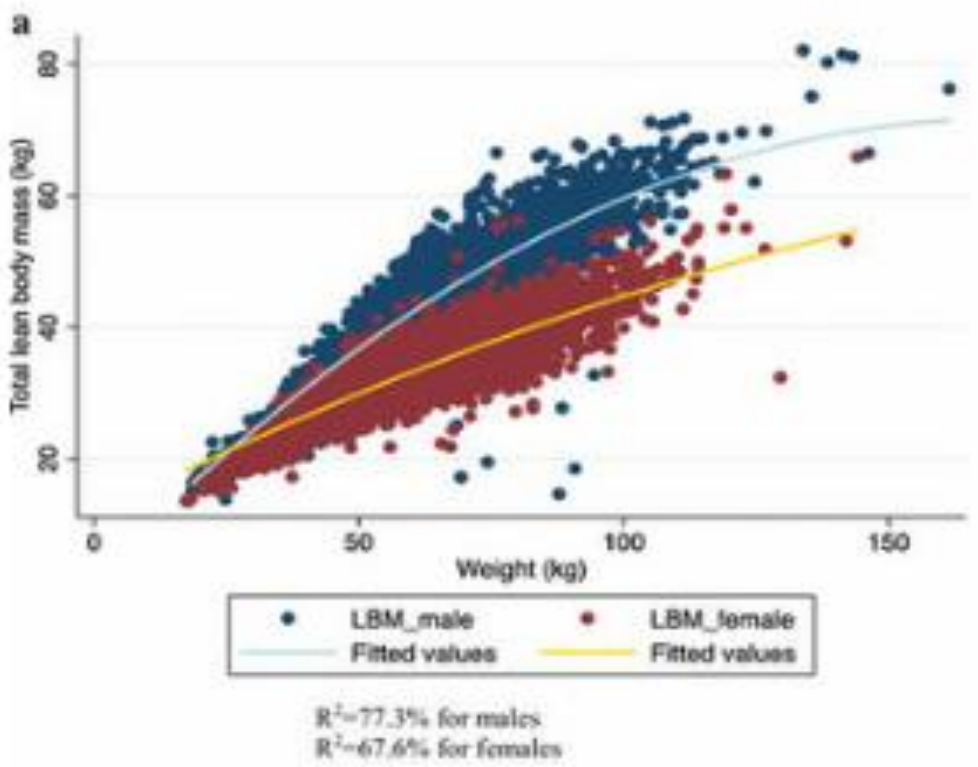
What about adverse effects?

Short term complications:

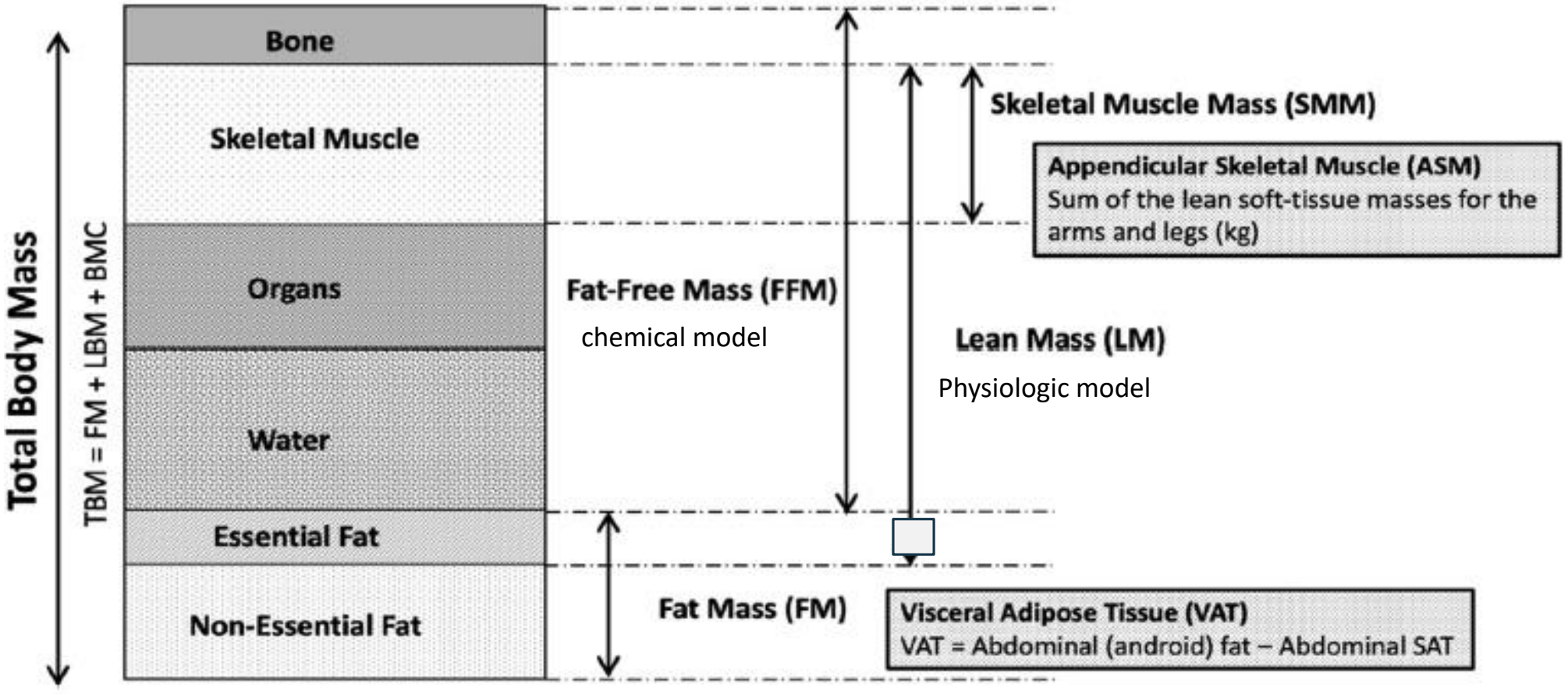
- GI

Long term complications:

- Bone
- Muscle

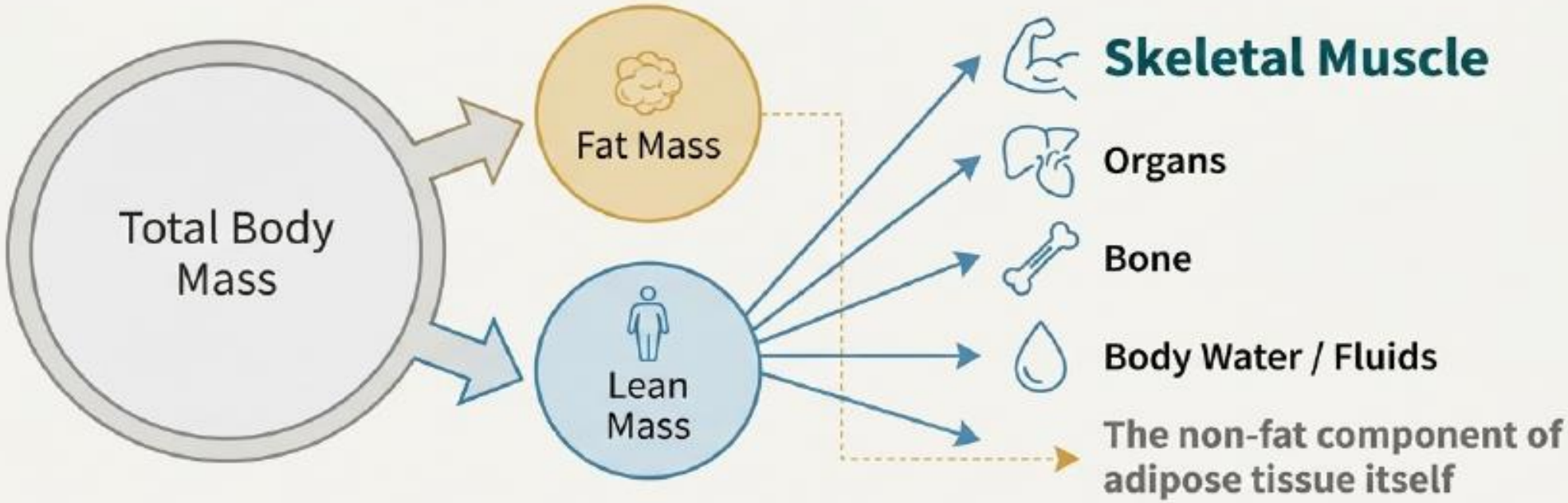


MUSCLE MASS VERSUS LEAN MASS AND GLP-1–BASED THERAPIES



The Problem Begins with the Measurement: 'Lean Mass' Is Not 'Muscle Mass'

Most major GLP-1 RA trials report on 'lean mass,' typically measured by DEXA. This metric is a composite and includes more than just muscle.



Critical Insight: Up to 15% of adipose tissue is fat-free/lean mass. Therefore, significant fat loss can directly contribute to a measured decrease in lean mass, inaccurately reflecting true muscle change.

Obese: **Lean mass** is often increased compared to normal weight individuals, mainly because the body needs more muscle to support the extra weight.
lean mass /total body weight ↓
(Despite higher absolute muscle mass, muscle quality and function may be impaired**)**.

doi:10.3945/an.116.014506.

Component	Normal Weight Person	Obese Person
Fat Mass	18–24% (M), 25–31% (F)	>25% (M), >32% (F), often much higher
Lean Mass	Majority of body weight	Increased in absolute terms, but lower percentage
Bone Mass	Normal for age/sex	Slightly increased

Muscle mass in PWO (Person with obesity)

- Association between body weight (also BMI) and muscle mass
- In PWO : muscle mass (total fat-free) **>** normal weight
- Weight loss (from any intervention) → loss of total body mass including muscle mass. (also during weight gain)
- Larger magnitudes of weight loss → ↑concern for potential adverse effects on muscle health(quantity, health, and function), especially in more vulnerable patients.

Weight loss- Body composition

Pharmacologic agent	Population	Measurement	Body weight change, %	Lean change, %
Semaglutide (STEP 1)[1]	BMI ≥30 or ≥27 kg/m^2 + comorbidity; no diabetes	DEXA (lean mass)	−14.9	−13.2*
Semaglutide (SUSTAIN 8)[25]	Type 2 diabetes	DEXA (lean mass)	−6.0*	−4.5*
Tirzepatide (SURMOUNT-1)[2]	BMI ≥30 or ≥27 kg/m^2 + comorbidity; no diabetes	DEXA (lean mass)	−20.9†	−10.9
Liraglutide + lifestyle (Neeland et al[26])	BMI ≥30 or ≥27 kg/m^2 + metabolic syndrome; no diabetes	MRI (lean volume)	−6.6	−2.5
Liraglutide (Lundgren et al[27])	BMI ≥32 kg/m^2; no diabetes	DEXA (lean mass)	−0.7*	0.0*
Liraglutide + exercise (Lundgren et al[27])			−3.5*	+0.8*

Circulation. 2024;150:1288–1298

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

Review & systematic review

Study (first author, year)	Population	Agent and dose	Duration	composition method	Main outcomes	Key takeaway
Wilding 2021 (STEP-1 exploratory)[29]	Adults with overweight/obesity	Semaglutide 2.4 mg QW	68 week	DXA	Larger FM than LBM reduction; relative %LBM increase	Weight loss predominantly from FM; absolute LBM decrease modest
McCrimmon 2020 (SUSTAIN-8 substudy)[30]	T2D on metformin	Semaglutide 1 mg QW vs. canagliflozin	52 week	DXA	Larger FM than LBM reduction; relative %LBM increase	Pattern FM loss > LBM loss replicated in T2D
Look 2025 (SURMOUNT-1 subanalysis)[31]	Adults with overweight/obesity	Tirzepatide 5/10/15 mg QW	72 week	DXA	≈75% of weight loss from FM; LBM decline modest	Robust FM loss with relatively smaller LBM loss
Jiao 2025 (meta-analysis)[32]	Mixed populations	GLP-1RA (various)	-	Mixed	Confirms predominant FM loss with modest absolute LBM decline; heterogeneity noted	Synthesis aligns with STEP/SUSTAIN patterns
Osaka 2023 (retrospective)[33]	Older adults with T2D	GLP-1RA (various) + supervised exercise	9 days	BIA	ASM improved in some patients despite weight loss	Suggests possible ASM preservation in specific settings (non-randomized)
Ozeki 2022 (pilot)[34]	Adults with obesity and T2D	Semaglutide	26 week	BIA	Weight and FM decreased; LBM/ASM changes small	Small pilot; direction consistent with FM ≫ LBM
Volpe 2022[36]	T2D	Semaglutide	26 week	BIA	Slight reduction in LBM; handgrip maintained	Function preserved despite modest lean mass decline
Ditzenberger 2025[37]	People with HIV and MASLD	Semaglutide	24 week	CT/MRI	Reduced psoas volume with weight loss; chair-stand/gait speed unchanged	Short-term weight loss without functional decline
Kosiborod 2023[38]	People with HFpEF and obesity	Semaglutide 2.4 mg	52 week	-	Higher improvement in the 6-min walk distance in the semaglutide group vs. placebo	Greater improvement in exercise function

Eur J Clin Invest. 2025;00:e70155.

US FDA:

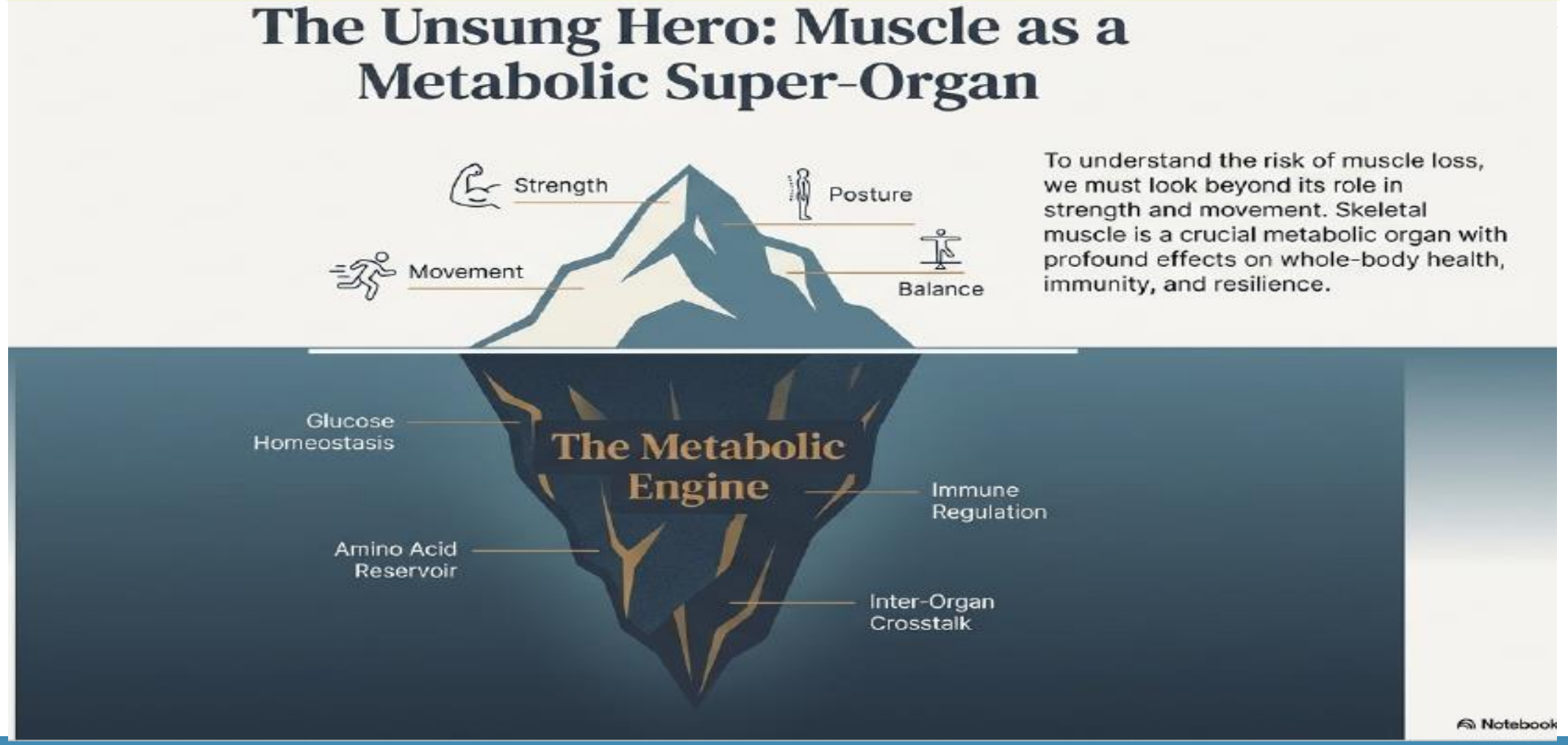
The only acceptable primary efficacy end points for weight loss drug trials changes in body weight

Body composition metrics, are considered safety end points,

- which require far smaller cohorts for testing
- does not require any tests of muscle function, mobility, or strength

➢ Investigations into body composition or muscle-related changes associated with GLP-1RAs are thus limited and likely underpowered and, consequently, the effect on muscle health and function is largely unknown.

Why Muscle Mass Matters?



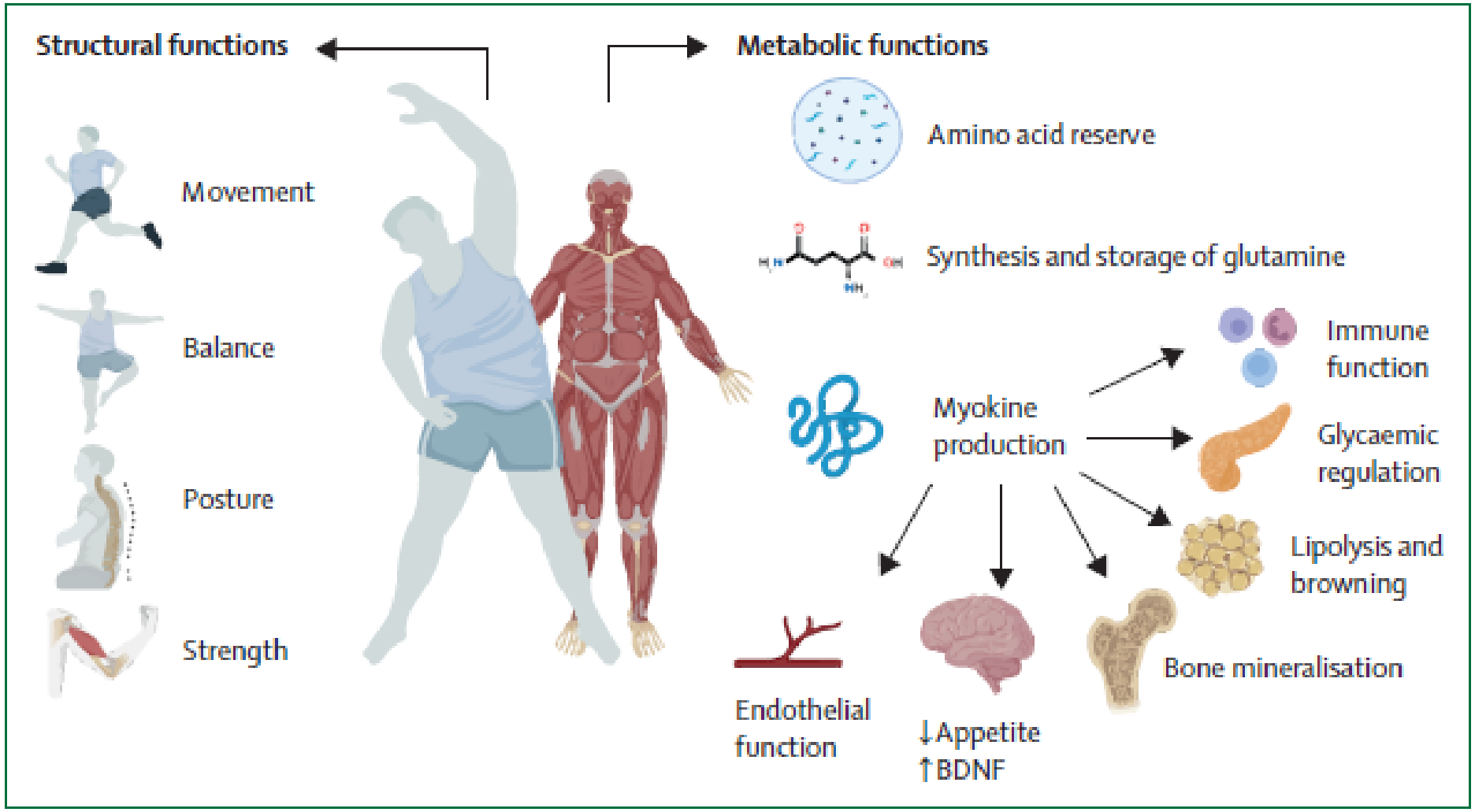


Figure: **Selected key roles of skeletal muscle as a structural versus metabolic organ**

Metabolic and immune system functions of muscle

- **Glucose regulation:** Muscle mass is central to glucose homeostasis, taking up glucose in response to insulin to maintain normal blood sugar.
- **Myokines:** Muscle cells release signalling molecules that act as endocrine factors, influencing systemic metabolism, energy balance, and inflammation.
- **Amino acid reservoir:** Muscle serves as a storehouse for amino acids, mobilized during stress, trauma, or infection.
- **Glutamine synthesis:** Muscle produces and stores glutamine, a key amino acid essential for nitrogen transport and immune system function.

Why Muscle Mass Matters?

Sarcopenic Obesity: The target population often has low muscle mass/high fat mass at baseline. Further muscle loss exacerbates this condition.

Functional Outcomes: Loss of muscle strength and mass (sarcopenia) increases risk of frailty, falls, functional decline, and hospitalization, especially in older adults.

Metabolic Health: Muscle is a primary site for glucose disposal and energy expenditure. Losing muscle can negatively impact metabolic rate and insulin sensitivity, potentially counteracting some benefits of weight loss.

Long-term Weight Maintenance: Lower resting metabolic rate from muscle loss may predispose to weight regain.

Why lean mass maintenance is important

Organ mass reduction: Weight loss decreases the size of organs like the liver, heart, and kidneys, which have a higher basal metabolic rate than skeletal muscle.

Drivers of reduced metabolism:

- 60% of the decline in basal metabolic rate comes from loss of total tissue mass (fat-free, fat, and organ tissue).
- 40% is due to metabolic adaptation (adaptive thermogenesis), where the body becomes more energy-efficient.

Why lean mass maintenance is important during weight loss?

Metabolic rate of muscles and internal organs **>** equivalent weight of fat. ↓ resting energy expenditure

- 1 Kg muscle mass loss → 13 Kcal/d
- 1 Kg fat mass loss → ≈4 Kcal/d
- Maintenance of lean body mass facilitates a higher metabolic rate and makes it easier to lose and maintain body weight during a weight loss intervention.
-

Whether loss of muscle mass associated with weight loss treatments such as GLP-1 RAs is

- **Maladaptive** (ie, adversely affecting muscle health or function)
- **Adaptive** (ie, a physiologic response to weight loss maintaining or minimally affecting muscle health or function)
- **Enhanced** (ie, improved muscle health or function after treatment)

Is Muscle Change a Sign of Harm or a Healthy Response?

The critical question is not *if* muscle mass is lost, but *what that loss signifies.*
We must discern between:

Maladaptive: An adverse change, negatively affecting muscle health or function.

Adaptive: A physiologic response to lower body weight, maintainig or minimally affecting muscle health.

Enhanced: An outright improvement in muscle health or function.

An Analogy: Left Ventricular Hypertrophy (LVH)

When hypertension is controlled, LV mass decreases. This is not a sign of a weaker heart, but a beneficial, **adaptive** normalization of cardiac muscle structure and function. Could the same principle apply to skeletal muscle during weight loss?

SKELETAL MUSCLE PHYSIOLOGY IN OBESITY AND IN WEIGHT LOSS

Muscle in obesity: People with obesity tend to have more muscle mass but relatively weaker strength, reduced mobility, and impaired function.

- Insulin sensitivity:
  - Weight gain → decreased sensitivity
  - Weight loss → improved sensitivity
- Lifestyle weight loss (~5%):
  - Leads to some lean mass loss
  - Improves insulin sensitivity in skeletal muscle, adipose tissue, and liver

➢ Reflects a shift toward better muscle quality despite lower quantity

Effect of diet-induced weight loss on muscle mass in PWO

Weight loss (8–10%) → muscle mass reduction of ~2–10% • Reduction reflects adjustment to lower body weight, not a harmful deficit

• Obese individuals start with greater muscle mass than normal-weight peers (No muscle deficit)

• Despite lean mass loss → improved fat-free mass / fat mass ratio

• **Overall: More favorable body composition after weight loss**

Effect of Bariatric Surgery-induced weight loss on muscle mass in PWO

Rapid, massive weight loss: >20% of total body weight

- Fat-free mass (FFM) loss not accelerated relative to fat or total body mass
- FFM contribution to total weight loss: <30%
- Post-surgery FFM/total body weight ratio: unchanged or even greater vs. matched controls
- Key point: **Bariatric surgery improves body composition** despite large weight reductions

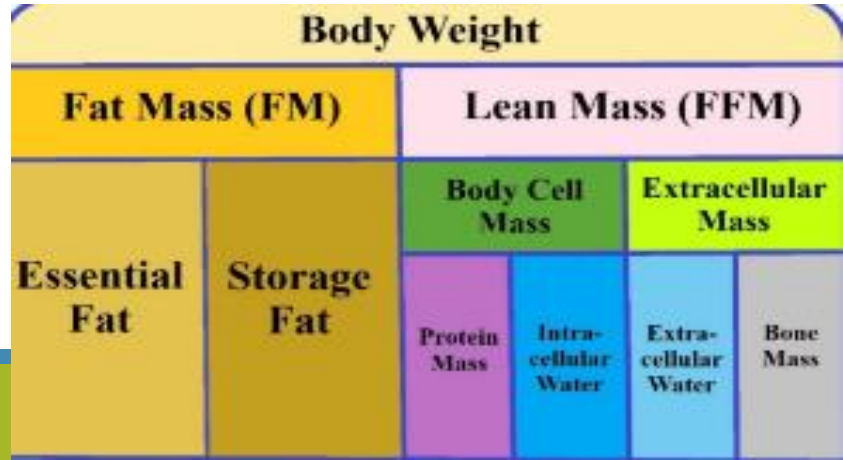
What do meta-analyses say?

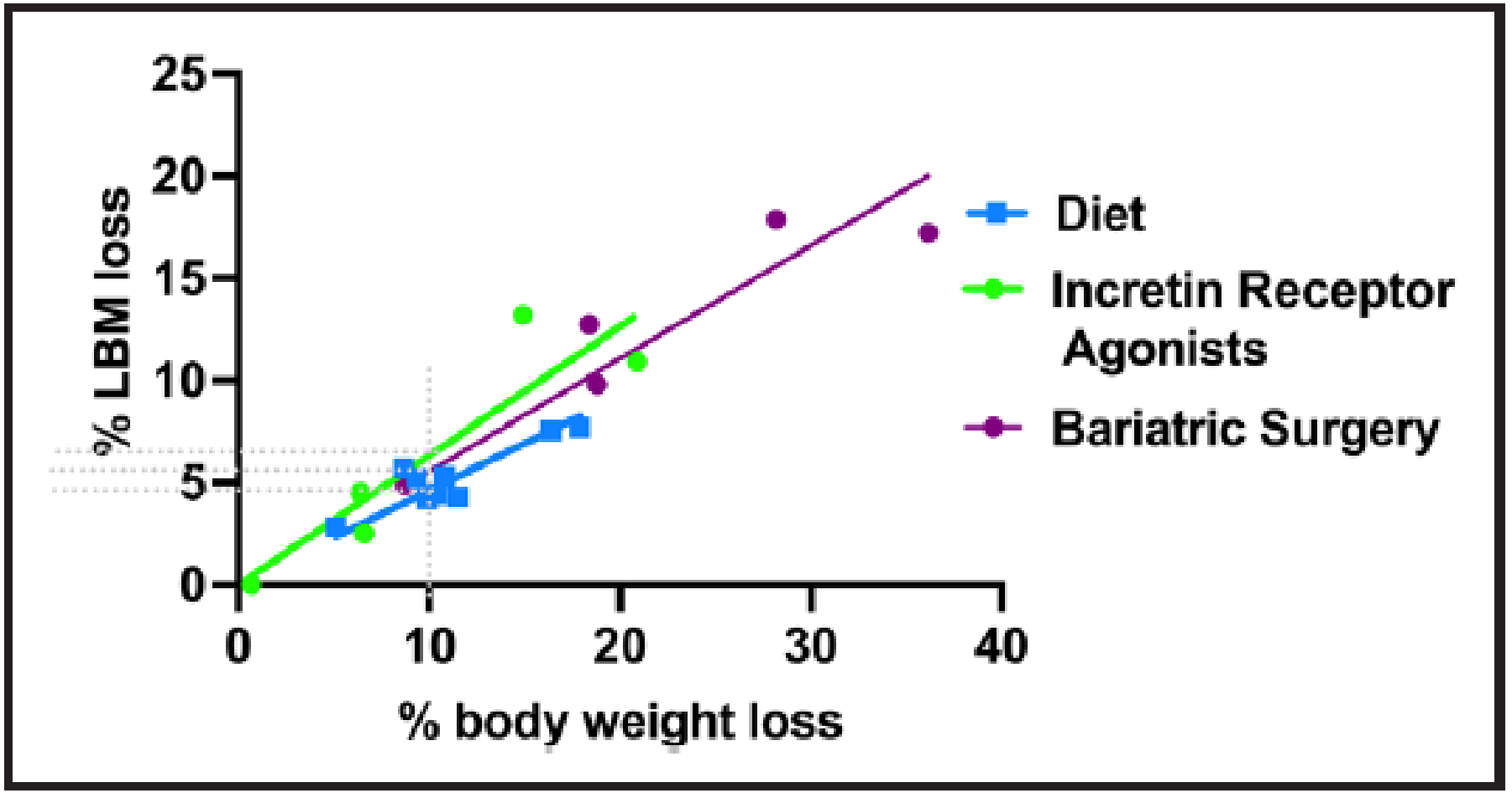
Lean mass: muscle + organs + bone + fluids and water in fat tissue

The proportion of weight loss from lean mass for

- Dietary, behavioural and pharmacological weight loss (26 cohorts) ranged from 5.9% to 26.1% and
- the effect from surgical weight loss (29 cohorts) from 19.2% to 23.6%.

A systematic review of the effects of GLP-1RAs and SGLT2 inhibitors on humans reported that 20%–50% of total weight loss was lean mass, with similar results for both GLP-1RAs and SGLT2 inhibitors.





The relationship of percent weight loss to percent loss of lean body mass resulting from dietary intervention, therapy with GLP-1 RA or GLP-1/GIP RA, or bariatric surgery in various studies.

Limits of Lean Mass Assessment

Lean mass ≠ muscle mass → cannot capture muscle composition or function

Measurement challenge: Lean mass changes don't directly reflect muscle health

Adipose tissue overlap: Up to **15%** **of fat tissue counts as lean mass**

Implication: Large fat loss can falsely appear as lean mass loss

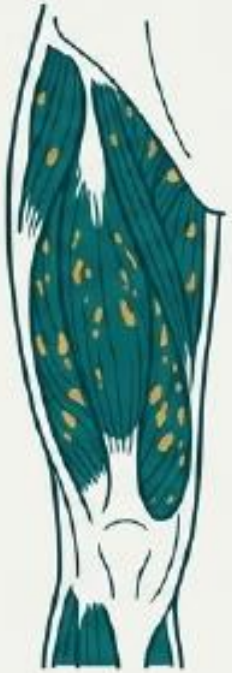
Key point: Lean mass reduction in weight loss trials may **misrepresent true muscle changes**

A More Precise Approach: Moving from 'Lean Mass' to Muscle Quantity and Quality

Advanced imaging with MRI or CT allows for a more accurate and comprehensive assessment of muscle health through two key metrics:

1. Muscle Volume Z-Score (Quantity)

- A personalized score that measures muscle volume in standard deviations from the mean for an individual's specific sex, height, and weight.
- It answers the question: "Is the amount of muscle appropriate for this person's body size?"



2. Muscle Fat Infiltration (Quality)

- Measures the amount of fat within the muscle tissue (myosteatosis).
- Lower fat infiltration is strongly linked to better muscle function, insulin sensitivity, and improved clinical outcomes.

Muscle mass, muscle quality and strength

Muscle mass is a poor predictor of muscle strength

Muscle mass ≠ strength: The amount of muscle does not reliably predict its ability to generate force.

- Composition differences: Variability in muscle tissue (e.g., fat or connective tissue deposits) affects functional capacity.
- Neuromuscular adaptations: Regular use or disuse alters neural activation and coordination, influencing strength independently of muscle size.

Muscle quality and muscle function in obesity

La fortuna et al. found

- A relation between adiposity and muscle lipid content (assessed by X-ray attenuation) in middle-aged and older men and women.

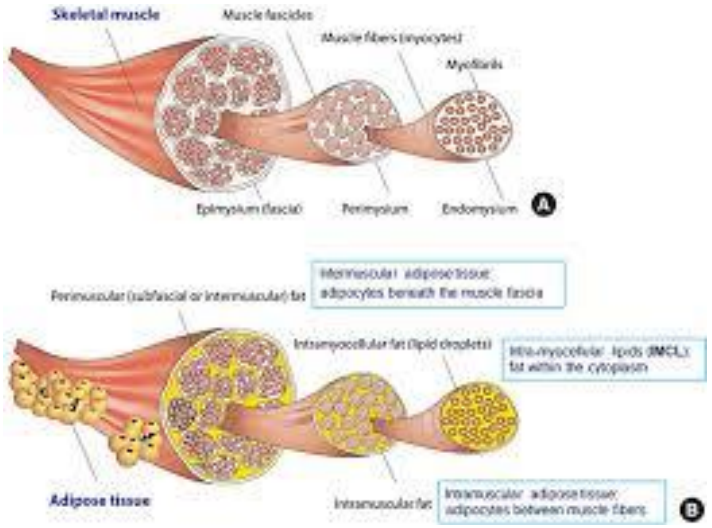
Choi et al. found that

- Older adults with obesity had ~20% more thigh muscle mass and ~2 times more muscle lipid content (assessed in vivo as ultrasound echo intensity) than older adults with normal weight.
- They also found that obesity was associated with reduced ex vivo single-myofiber function (peak Ca2+-activated force) and in vivo muscle function (peak torque)

SKELETAL MUSCLE PHYSIOLOGY IN OBESITY AND IN WEIGHT LOSS

Quantity (size and number of myocytes [ie, hypertrophy versus hyperplasia])

- **Quality** (composition)- (myosteatosis and muscle fiber composition)
  - those living with obesity have more muscle mass but greater relative weakness, as well as reduced mobility and function



Muscle health

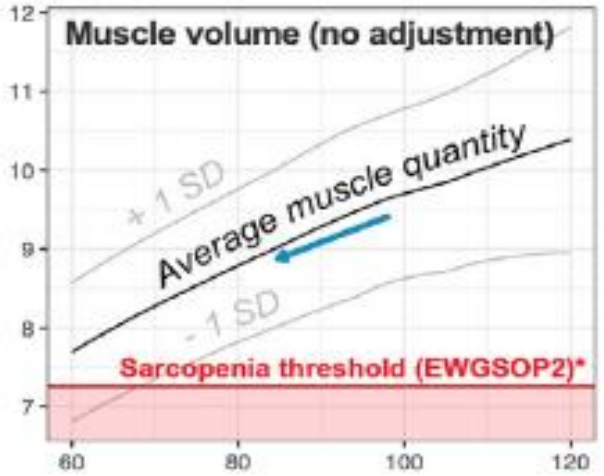
Quantity

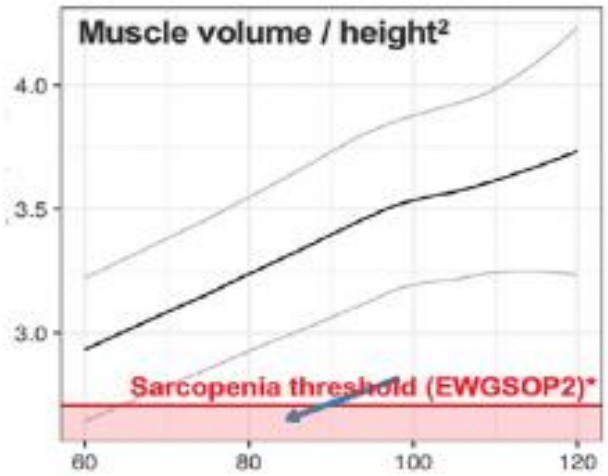
- Absolute
- Relative

Quality

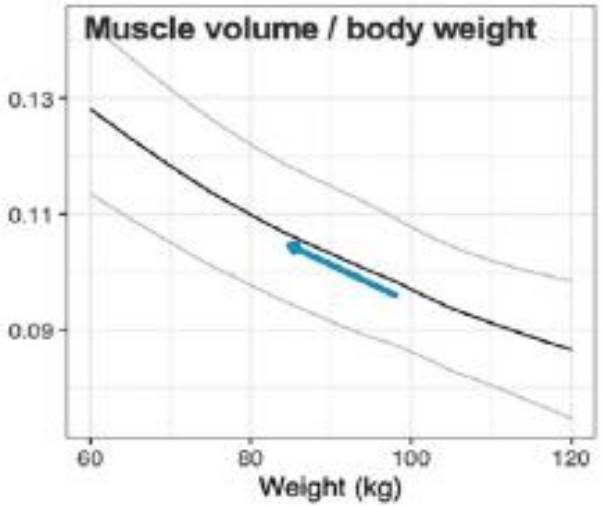
Function or performance

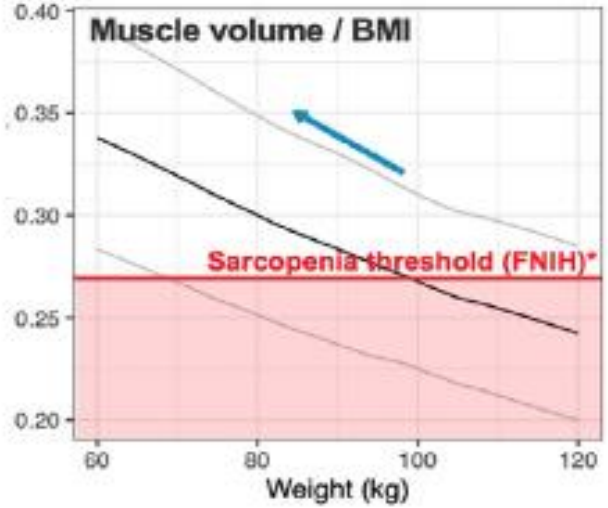
(A)





Muscle quantity loss in line with weight loss. No body size normalization or division by height² leads to a conclusion of **decreased 'muscle quantity'** and a **trajectory towards sarcopenia**.





Muscle quantity loss in line with weight loss. Division by body weight or BMI leads to a conclusion of **increased 'muscle quantity'** and a trajectory **away from sarcopenia**.

A BETTER DESCRIPTION OF MUSCLE HEALTH: MUSCLE VOLUME Z-SCORE AND MUSCLE FAT INFILTRATION

Muscle volume Z score-Reference standard

To more accurately describe "**adequate muscle mass**" within obesity and provide a measurement of muscle quantity that is not confounded by the individual's body.

- A value = 0 indicates a muscle volume as expected given sex and body size
- Muscle volume z-score improves the association with muscle function and mobility, and associates with morbidity and mortality.

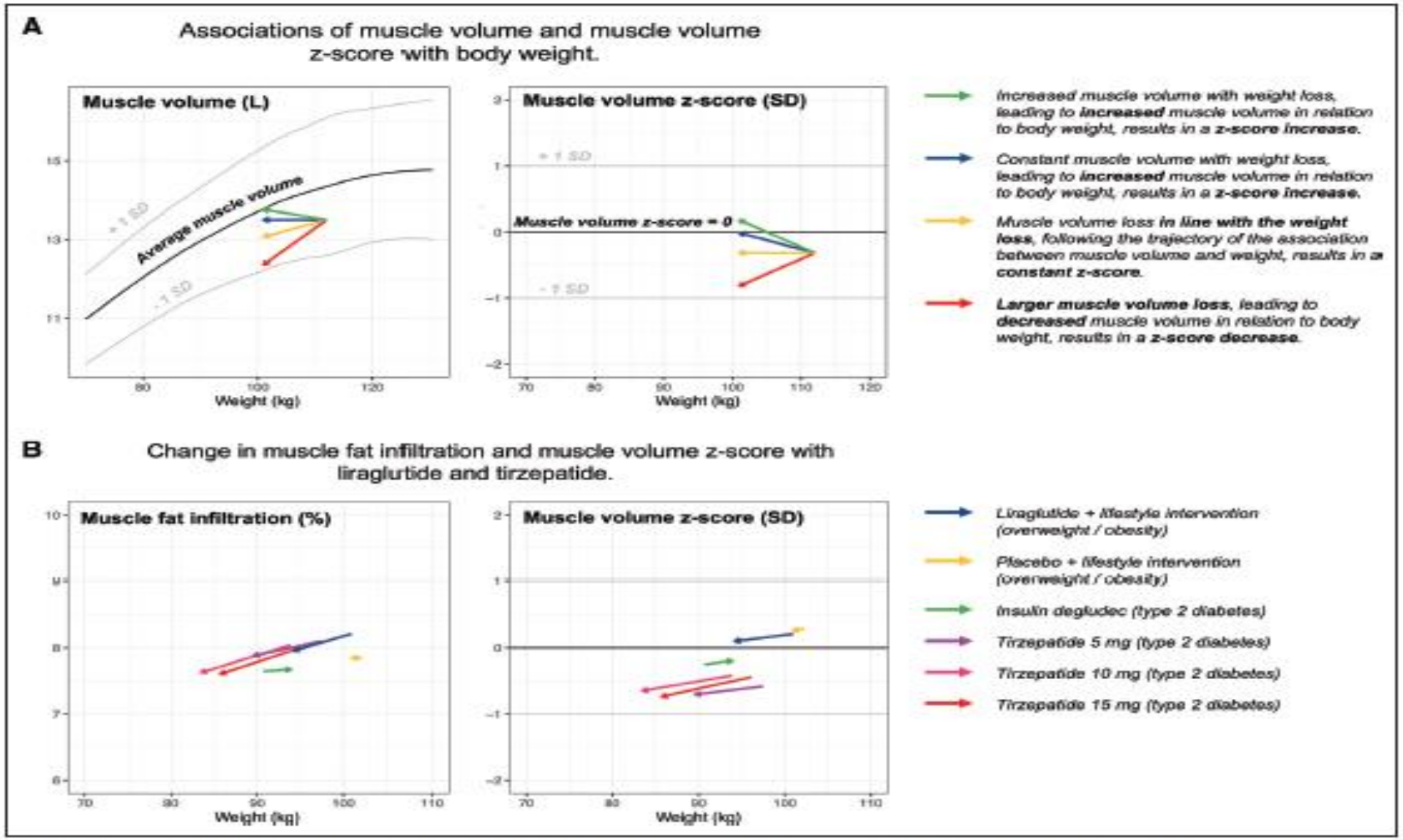


Figure 3. Conceptual description of how changes in muscle volume (in liters) relate to changes in muscle volume z-score, and reported changes in muscle composition from liraglutide and tirzepatide treatment.

The Verdict from Advanced Imaging: What MRI Studies of GLP-1 RAs Reveal

Recent MRI-based studies of Liraglutide and Tirzepatide provide a clearer picture of muscle changes.

Liraglutide	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Body Weight Change % ↓ -6.6%	Body Weight Change % ↓ -8.0%	Body Weight Change % ↓ -10.5%	Body Weight Change % ↓ -11.7%
Muscle Volume Z-Score Change (SD) → -0.11 SD	Muscle Volume Z-Score Change (SD) → -0.12 SD	Muscle Volume Z-Score Change (SD) → -0.23 SD	Muscle Volume Z-Score Change (SD) → -0.30 SD
Muscle Fat Infiltration Change (% points) ↓ -0.26 pp	Muscle Fat Infiltration Change (% points) ↓ -0.23 pp	Muscle Fat Infiltration Change (% points) ↓ -0.42 pp	Muscle Fat Infiltration Change (% points) ↓ -0.44 pp

Study description			Weight change, %	Muscle composition change, mean (SD)		
Study	Population	Group		Muscle volume, L	Muscle volume z-score, SD	Muscle fat infiltration, pp
Liraglutide (Neeland et al[26])	BMI ≥30 or ≥27 kg/m² + metabolic syndrome, no diabetes	Liraglutide + lifestyle intervention	−6.6	−0.35 (0.35)*	−0.11 (0.31)*	−0.26 (0.43)*
		Placebo + lifestyle intervention	−1.2	−0.06 (0.38)	−0.03 (0.37)	−0.01 (0.58)
Tirzepatide (SURPASS-3 MRI)[68,69]	Type 2 diabetes, BMI ≥25 kg/m²	Tirzepatide 5 mg	−8.0	−0.44 (0.57)*	−0.12 (0.33)*	−0.23 (0.77)*
		Tirzepatide 10 mg	−10.5	−0.71 (0.74)*	−0.23 (0.48)*	−0.42 (0.61)*
		Tirzepatide 15 mg	−11.7	−0.76 (0.74)*	−0.30 (0.47)*	−0.44 (0.81)*
		Insulin degludec	+2.3	+0.16 (0.54)	+0.06 (0.43)	+0.03 (0.40)

The Response is Adaptive: Muscle Loss is Proportional and Quality Improves

Quantity is Proportional

The changes in muscle volume z-score are small, indicating that muscle volume loss is largely commensurate with what is expected given the substantial weight loss achieved.

Quality is Enhanced

Both Líraglutide and Tirzepatide led to a significant **reduction** in muscle fat infiltration.

> **Critical Context:** This improvement in muscle quality is opposite to the effect of normal aging, where muscle fat infiltration typically increases by ~0.11 percentage points annually. The treatment effectively reverses an age-related decline in muscle quality.

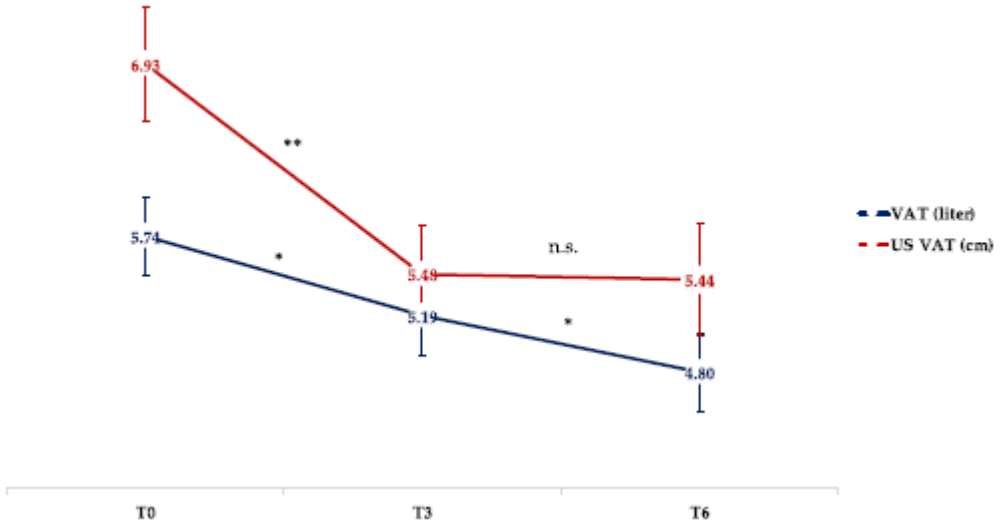
nutrients

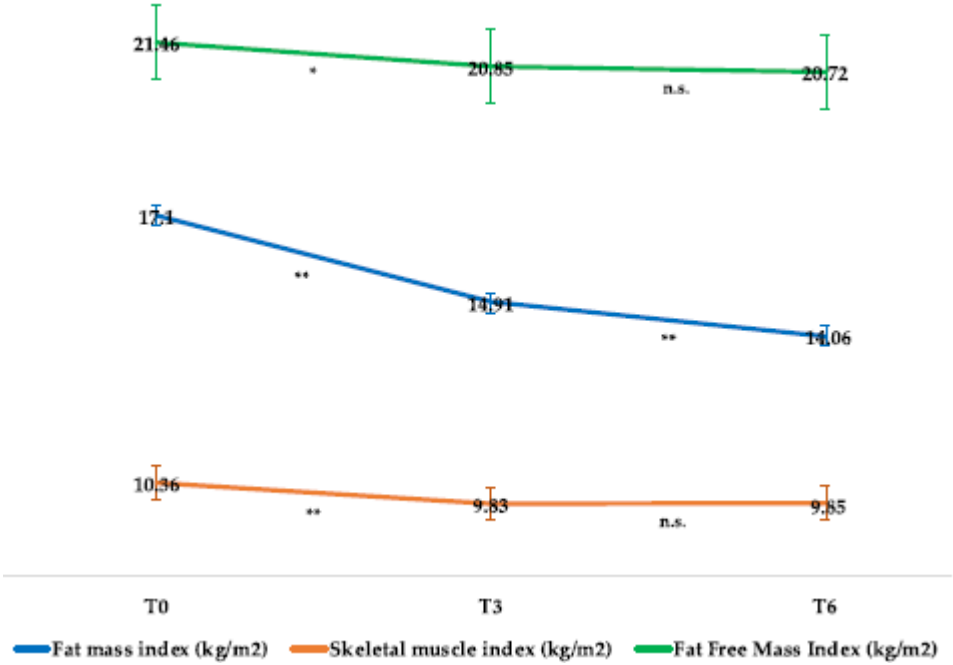
MDPI

Article

Once-Weekly Semaglutide Induces an Early Improvement in Body Composition in Patients with Type 2 Diabetes: A 26-Week Prospective Real-Life Study

A total of 180 patients with T2D (mean age 64.9 ± 10.8 years; men 60.2%) who attended our clinic





Parameters	Time		
	T0	Variation at T3	Variation at T6
Body weight (kg)	103.96 ± 3.03	−7.83 ± 0.72 **	−9.89 ± 0.99 ** #
Body mass index (kg/m^2)	38.81 ± 1.18	−3.05 ± 0.30 **	−3.36 ± 0.42 **
Waist circumference (cm)	123.53 ± 2.24	−6.32 ± 1.12 **	−7.31 ± 1.15 **
Fasting glycemia (mg/dL)	129.95 ± 5.71	−15.57 ± 4.41 **	−23.56 ± 4.45 ** ##
HbA_{1c} (mmol/mol)	52.86 ± 3.36	−10.72 ± 2.80 **	−11.16 ± 2.99 **
Serum creatinine (mg/dL)	0.88 ± 0.04	0.03 ± 0.03	0.01 ± 0.03
eGFR (mL/min/1.73 m^2)	87.85 ± 3.57	0.85 ± 2.55	−2.02 ± 2.52
Fasting serum insulin (mUI/L)	22.59 ± 2.46	−0.76 ± 3.17	−5.22 ± 2.16 *
Fasting serum C-peptide (ng/mL)	3.72 ± 0.24	0.08 ± 0.29	−0.13 ± 0.27
HOMA-IR index	6.88 ± 0.77	−1.22 ± 1.06	−2.62 ± 0.79 **
Visceral adipose tissue (L)	5.74 ± 0.45	−0.55 ± 0.27 *	−0.95 ± 0.24 * #
Fat mass index (kg/m^2)	17.10 ± 0.99	−2.19 ± 0.46 **	−3.04 ± 0.43 ** #
Fat-free mass index (kg/m^2)	21.45 ± 0.47	−0.61 ± 0.24 *	−0.74 ± 0.17 **
Skeletal muscle mass (kg)	28.16 ± 0.98	−1.31 ± 0.37 **	−1.53 ± 0.36 **
Skeletal muscle index (kg/m^2)	10.36 ± 0.27	−0.52 ± 0.14 **	−0.51 ± 0.14 **
HG (kg)	32.49 ± 1.64	0.49 ± 1.75	0.76 ± 1.26
MQI (kg/kg)	1.06 ± 0.09	0.16 ± 0.09	0.17 ± 0.08

Maintain or increase muscle mass

- **Increasing physical activity during weight loss**
  - Physical activity alone may not fully protect against reduction in LBM
  - Both **endurance** and **resistance-type** exercise help preserve muscle mass during weight loss, resistance-type exercise also improves muscle strength

Effects of exercise training on muscle mass

The effect of endurance-type exercise training on muscle mass during weight-loss therapy, is less clear

Resistance-type exercise is an effective strategy to attenuate or even prevent the weight-loss–induced loss of muscle mass during weight loss

Effect of high-protein intake on lean body and muscle mass

- **GLP-1 treatments**: Moderate protein increase is especially important, as these therapies may reduce intake of high-quality protein.
- During weight maintenance/gain: Extra protein beyond the RDA does not improve fat-free or muscle mass.
- During weight loss: Higher protein intake shows a small but significant benefit, preserving about 400–800 g of lean mass.

Daily protein intake and its distribution

As important as total daily protein intake could be the distribution of dietary protein intake over the course of the day (evenly throughout the day more effective!)

A refractory period during which muscle protein synthesis, once stimulated by amino acids, cannot be stimulated again ("muscle-full" phenomenon)

This matter needs more study

Protein intake concern

Protein supplementation of a hypocaloric diet eliminates the weight-loss–induced improvement in muscle insulin sensitivity (assessed by using the hyperinsulinemic-euglycemic clamp procedure), even though weight loss was the same (10%) in both the high-protein and standard-protein diet groups.

Protein intake concern

Protein Supplementation & Insulin Sensitivity

- Hypocaloric diet + protein supplementation: Both high-protein and standard-protein groups lost the same amount of weight (~10%).
- Key difference: In the high-protein group, the usual improvement in muscle insulin sensitivity seen with weight loss was eliminated.
- Implication: Extra protein during calorie restriction may blunt metabolic benefits of weight loss, despite equal fat reduction.

Pharmacologic treatments

- **GH** & **Recombinant GHRH**:
  - ↓ visceral adipose tissue mass & ↑ lean body mass
  - GH-related drugs are expensive / considerable treatment-associated side effects, including arthralgias, myalgias, peripheral edema, insulin resistance, and type 2 diabetes.
  - Long-term safety?
- Other targets for muscle health include the **activin type II receptor**
  - Activin A: Garetosmab (antia-ctivin A)
  - Myostatin: Trevogrumab (anti-myostatin)
- Bimagrumab is a human monoclonal antibody that binds to activin type II receptor, preventing the action of the natural ligands.

New promise:

Study of semaglutide combined with trevogrumab (**antimyostatin**) and garetosmab (**antiactivin A**) in primates with obesity showed large fat mass loss with an increase of lean mass.

Other targets, such as **urocortin 2** and **urocortin 3**

Thus, combination of targets for muscle health + drugs reducing food intake (such as GLP-1–based treatments) appear to be an intriguing option to generate therapies that potentially reduce fat mass while increasing muscle mass and, in theory, induce more sustainable weight loss.

The Horizon: Engineering Better Body Composition Outcomes

*The future of obesity pharmacotherapy lies in combination approaches that **uncouple fat** loss from muscle loss.*

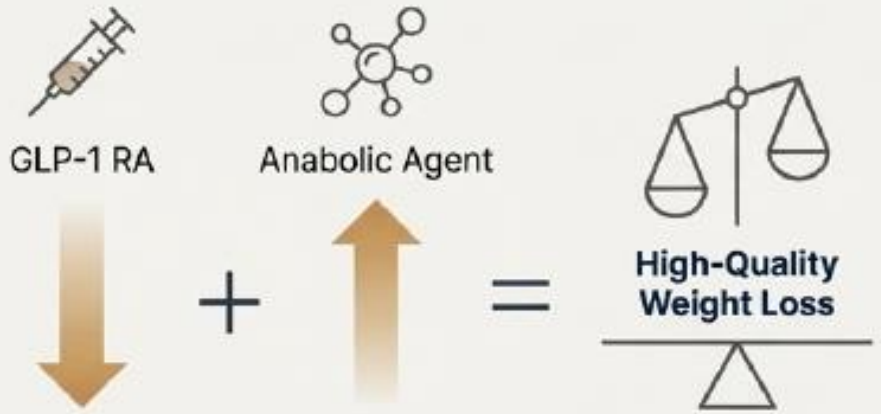
Agents Under Investigation

Bimagrumab: A monoclonal antibody that blocks Activin Type II receptors, preventing negative regulators like myostatin from inhibiting muscle growth.

In a Phase 2 trial, bimagrumab alone increased lean mass by 3.6% while decreasing fat mass by 20.5%.

Other Targets: Selective androgen receptor modulators (SARMs) like enobosarm are also being explored.

Combining Catabolic and Anabolic Signals



Preclinical Promise

A study in primates combining semaglutide with myostatin inhibitors resulted in large fat mass loss with an increase in lean mass.

This demonstrates a powerful proof-of-concept for achieving high-quality weight loss.

The Next Frontier: Combining Fat Reduction with Muscle Preservation

The future of metabolic therapy may lie in combining GLP-1-based drugs with agents that directly target muscle anabolism.

Emerging Targets Under Investigation

- Activin Type II Receptor Antibodies (e.g., Bimagrumab): In one trial, bimagrumab decreased fat mass by 20.5% while **increasing lean mass by 3.6%**.
- Myostatin Inhibitors (e.g., Trevogrumab): Preclinical data in primates shows combining semaglutide with myostatin/activin A inhibitors leads to large fat mass loss with an **increase in lean mass.**

Vision for the Future: Therapies that not only reduce fat mass but actively build or preserve muscle, potentially leading to more effective and sustainable weight loss.

Take home message

During intentional weight loss we loss lean body mass including muscle mass

Muscle health is important

- Structural & Functional
- Metabolic

Muscle heath measurement is a challenge

Quantitative- MRI , CT scan- (DEXA, BIA-Lean body mass)

Qualitative & Functional (Composition, Strength)-MRI , CT scan- Hand grip , …

Introduction of more objective and comprehensive ways of assessing muscle health (including accurate and meaningful assessments of muscle quantity, composition, function, mobility, and strength) is important.

Skeletal muscle changes with GLP-1 RA treatments

Adaptive: changes in muscle volume z-score indicate a change in muscle volume that is commensurate with what is expected given aging, disease status, and weight loss achieved,

Improvement in insulin sensitivity and muscle fat infiltration likely contributes to an adaptive process with improved muscle quality, lowering the probability for loss in strength and function.

Improving muscle quality, rather than preserving or increasing muscle mass, should therefore be the primary focus of therapeutic strategies for people with obesity.

Take home message

Maintain or increase muscle mass

- **Nonpharmacologic**
  - Increasing physical activity during weight loss
  - Moderate increase in protein intake
- **Pharmacologic treatment**
  - GH
  - GHRH
  - Activin II receptor blockade
  - Urocortin 2 and Urocortin 3

Thank you for your attention

A New Perspective on Muscle Health in Obesity Treatment

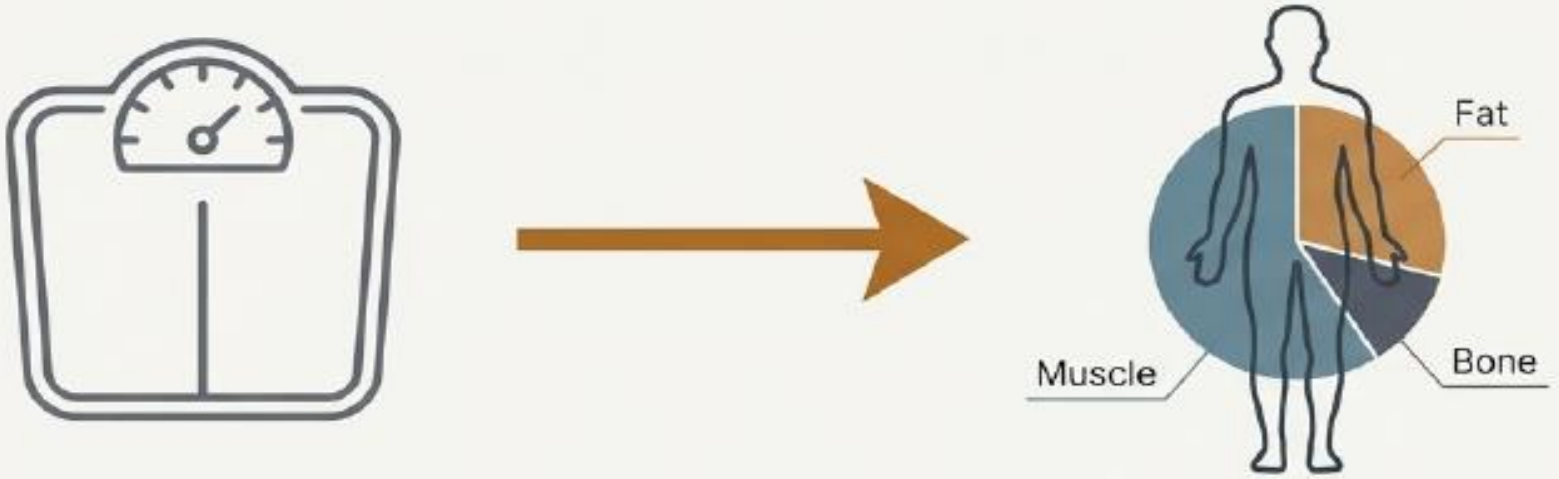
1. **The Concern was Valid, but the Metric was Flawed**: Initial alarms were based on 'lean mass,' an imprecise proxy for muscle.

2. **Advanced Imaging Provides Clarity**: MRI-based muscle volume z-score (quantity) and fat infiltration (quality) offer a superior assessment.

3. **The Evidence Points to Adaptation**: With GLP-1 RAs, muscle loss is proportional to weight loss, and muscle quality demonstrably improves.

The conversation must shift from a narrow focus on lean mass preservation to a more holistic and clinically meaningful goal: **optimizing muscle quantity, quality, and function** for the substantial number of patients who will benefit from these transformative therapies.

From Weight Loss to Quality Weight Loss



The goal is not to abandon these revolutionary medications, but to use them more intelligently. We must shift the clinical focus from the number on the scale to the quality of the weight lost, optimizing body composition to ensure long-term health and resilience.

Focus is placed on the complex interplay between muscle quantity, composition,

and function with metabolic physiology and the effect of GLP-1–based treatments, as well as challenges and opportunities for assessing muscle health and sarcopenia during weight loss.

Effects of obesity and weight loss on muscle mass, muscle strength, and global physical function

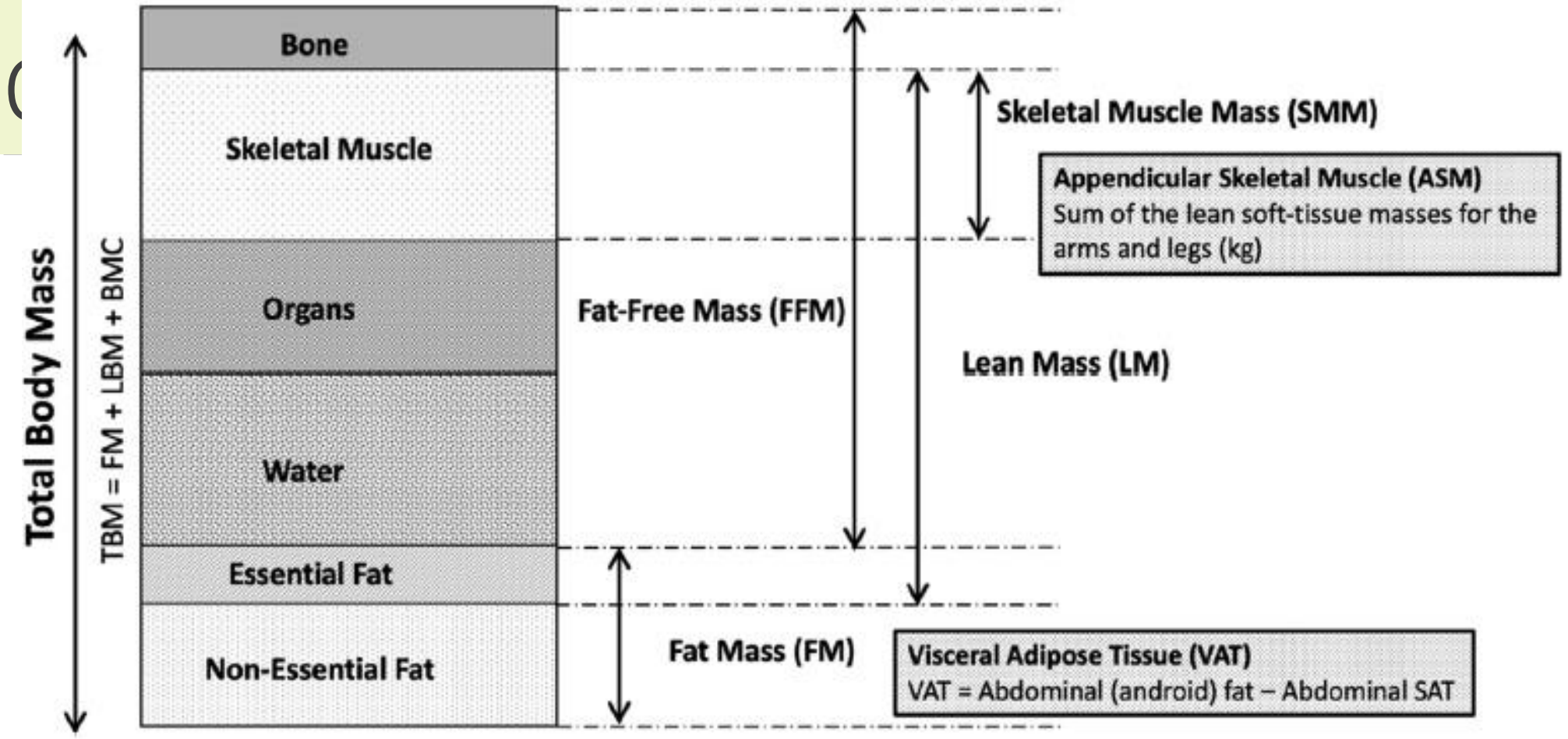
		Weight loss		
			CR with increased muscle activity	
	Obesity	CR	CR + HP	Endurance exercise or PA	Resistance exercise
Muscle mass	O > L	↓↓	↓	↓	↔
Muscle strength[2]	O < L	↔	↔	↔	↑
Global physical function	O < L	↑	↑	↑↑	↑↑

CR, calorie restriction; HP, high protein; L,lean; O, obese; PA, physical activity

Obese: **Lean mass** is often increased compared to normal weight individuals, mainly because the body needs more muscle to support the extra weight.
lean mass /total body weight ↓
(Despite higher absolute muscle mass, muscle quality and function may be impaired**)**.

doi:10.3945/an.116.014506.

Component	Normal Weight Person	Obese Person
Fat Mass	18–24% (M), 25–31% (F)	>25% (M), >32% (F), often much higher
Lean Mass	Majority of body weight	Increased in absolute terms, but lower percentage
Bone Mass	Normal for age/sex	Slightly increased
Water %	50–60% of body weight	45–55% of body weight
Metabolic Risk	Low	High



Fat free mass: Male > female

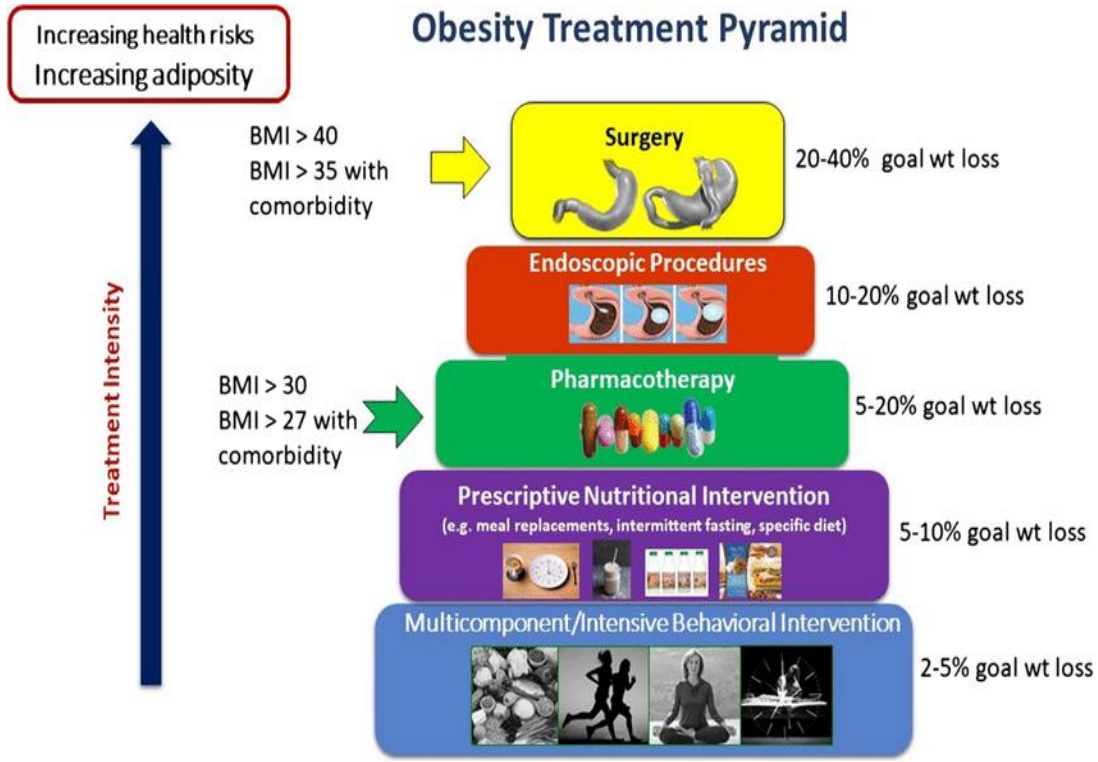
Weight reduction strategies:

Lifestyle:

- MNT
- Physical activity
- Behavioral Therapy

Pharmacotherapy

Bariatric Surgery



Concerns during Weight loss

Potential adverse effects of greater weight loss on

- Muscle quantity (mass)
- Health and function, especially in more vulnerable patients

Lean body mass, although contentious, is widely used as a surrogate measurement for muscle mass

Summary of GLP-1 RA Effects on Lean Mass and Volume in Randomized Clinical Trials

Pharmacologic agent	Population	Measurement	Body weight change, %	Lean change, %
Semaglutide (STEP 1)[1]	BMI ≥30 or ≥27 kg/m^2 + comorbidity; no diabetes	DEXA (lean mass)	−14.9	−13.2*
Semaglutide (SUSTAIN 8)[25]	Type 2 diabetes	DEXA (lean mass)	−6.0*	−4.5*
Tirzepatide (SURMOUNT-1)[2]	BMI ≥30 or ≥27 kg/m^2 + comorbidity; no diabetes	DEXA (lean mass)	−20.9†	−10.9
Liraglutide + lifestyle (Neeland et al[26])	BMI ≥30 or ≥27 kg/m^2 + metabolic syndrome; no diabetes	MRI (lean volume)	−6.6	−2.5
Liraglutide (Lundgren et al[27])	BMI ≥32 kg/m^2; no diabetes	DEXA (lean mass)	−0.7*	0.0*
Liraglutide + exercise (Lundgren et al[27])			−3.5*	+0.8*

Effect of diet-induced weight loss on muscle quality, muscle strength, and physical function

Diet-induced weight loss → ↓muscle lipid content

Grip strength and global measures of physical function, such as balance, walking speed, or climbing stairs, improve after weight loss

weight loss, despite causing loss of muscle mass, has beneficial effects on muscle quality and improves overall physical function.

Table 2. Summary of GLP-1 RA Effects on Muscle Volume, Muscle Volume z-score, and Muscle Fat Infiltration Quantified by MRI in Randomized Clinical Trials

Study description				Muscle composition change, mean (SD)		
Study	Population	Group	Weight change, %	Muscle volume, L	Muscle volume z-score, SD	Muscle fat infiltration, pp
Liraglutide (Neeland et al[26])	BMI ≥30 or ≥27 kg/m² + metabolic syndrome, no diabetes	Liraglutide + lifestyle intervention	−6.6	−0.35 (0.35)*	−0.11 (0.31)*	−0.26 (0.43)*
		Placebo + lifestyle intervention	−1.2	−0.06 (0.38)	−0.03 (0.37)	−0.01 (0.58)
Tirzepatide (SURPASS-3 MRI)[68,69]	Type 2 diabetes, BMI ≥25 kg/m²	Tirzepatide 5 mg	−8.0	−0.44 (0.57)*	−0.12 (0.33)*	−0.23 (0.77)*
		Tirzepatide 10 mg	−10.5	−0.71 (0.74)*	−0.23 (0.48)*	−0.42 (0.61)*
		Tirzepatide 15 mg	−11.7	−0.76 (0.74)*	−0.30 (0.47)*	−0.44 (0.81)*
		Insulin degludec	+2.3	+0.16 (0.54)	+0.06 (0.43)	+0.03 (0.40)

Reasons for the heterogeneity

1. The specific, individual physiological effects of different molecules
2. Heterogeneity in dosing leading to different weight loss kinetics
3. Varying duration of studies
4. Methodological heterogeneity and bias in lean mass assessments
5. Different patient populations (e.g., with vs. without diabetes)
6. Different lifestyle interventions concomitantly prescribed with the pharmacological intervention.

خاک هنر خیز من ای اصفهان
ای به هنر سرمه چشم جهان

زرکش وزربفت تو چون شاهکار
بافته بر حافظه ی روزگار

مسجدشه بین وشبستان او
نقش جهان سردرایوان او

هرکه درآنجا به تماشا رود
پای ندارد به دگرجا رود

مسرور اصفهانی

Protein Distribution & Muscle Synthesis

- Protein distribution matters: Evenly spreading protein intake across meals may be more effective than uneven intake.
- Muscle-full phenomenon: After stimulation by amino acids, muscle protein synthesis enters a refractory period and cannot be re-stimulated immediately.
- Research gap: More studies are needed to fully understand the impact of protein timing and distribution on muscle health.

Strategies to prevent the weight-loss–induced loss of muscle mass

- Regular physical activity, especially resistance-type exercise training,
- High protein intake
  - (1.25–1.5 times the RDA for sedentary persons
  - >1.5 times the RDA for those who exercise)
- the major regulators of muscle protein synthesis and breakdown
  - **dietary amino acids** (dietary protein)- dose-dependent manner
  - **Insulin**: potent inhibitor of muscle protein breakdown
  - **contractile activity:** (both resistance and endurance type) improves insulin sensitivity and stimulates muscle protein synthesis

Quarter FFM rule

The expected loss of FFM for a given amount of body weight loss that is commonly used as a reference for lean mass loss

This rule, called the quarter FFM rule: approximately 1/4 of weight loss will be FFM (i.e., ΔFFM/Δ Weight = ∼0.25), with the remaining three-quarters being fat mass.

Mechanisms responsible for loss of muscle mass during diet-induced weight-loss–protein synthesis versus breakdown

Calorie restriction decreases the postprandial rate of muscle protein synthesis and decreases or does not change the basal rate of muscle protein synthesis

Prolonged moderate calorie restriction and 5–10% weight loss → ↑ rate of muscle protein synthesis

The loss of muscle mass during prolonged moderate calorie restriction is therefore mediated by increased muscle proteolysis rather than muscle protein synthesis

Muscle protein synthesis (Basal & Postprandial) ↔ Muscle proteolysis

Potential novel dietary interventions to improve muscle mass, muscle strength, and physical function during weight loss

vitamin D,

fish-oil–derived n–3 FAs,

β-hydroxy-β-methylbutyrate

Fish-oil–derived n–3 FA supplementation has been shown to improve muscle mass, strength, and physical function in weight-stable older adults (130, 131); and β-hydroxy-β-methylbutyrate, a metabolite of leucine, improved both muscle mass and strength in healthy young and older adults .

However, their effects on muscle mass and strength during weight loss are not known.

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

concept of ‘relative or adequate muscle mass’

Accumulating evidence suggests that using the muscle volume z-score improves the association with muscle function and mobility, and is associated with morbidity and mortality

With more advanced imaging (MRI or computed tomography [CT]), in addition to more accurate and precise measures of muscle mass (rather than lean mass), it is also possible to achieve accurate measurements of muscle fat infiltration (indicating muscle quality).

reported associations indicate a stronger link of muscle fat with adverse outcomes as compared with muscle quantity

However, muscle quantity (mass/volume) and muscle fat are weakly correlated and seem to represent two different biological processes involved in muscle wasting. Therefore, a combined assessment provides a more complete description of muscle health that has been shown to improve the performance in identifying high-risk individuals.

Immune system functions of muscle

Low muscle mass is associated with

- Decreased immunity
- Increased risk of infections
- Reduced wound healing

Drug-induced weight loss without concurrent strategies to prevent substantial muscle loss can lead to, or exacerbate, sarcopenic obesity across the lifespan.

Sarcopenic obesity is prevalent and linked to poor health outcomes, such as increased risk of cardiovascular disease and higher morality rates.

Furthermore, many individuals seek to discontinue GLP-1 receptor agonists after initial weight loss, often due to weight loss plateau or loss of insurance coverage. In general, subsequent weight regain usually increases fat mass rather than muscle mass. (Drug induced > Diet induced weight loss?) => Sarcopenic obesity?

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

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

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

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

Given the consistent association between muscle volume and body weight, a reduction in muscle volume is expected during successful weight loss with GLP-1-based therapies. The more modest effects of liraglutide and tirzepatide on muscle volume z-score indicate that the muscle volume lost is, in large part, in line with what was expected due to the observed weight loss. Concomitantly, these therapies successfully reduced muscle fat infiltration and led to a robust reduction in the proportion of participants with adverse muscle composition.

When BW is reduced through dietary energy restriction, not all of the resulting weight loss can be attributed to fat mass (FM), with approximately **25% to 33%** estimated to comprise of reductions in lean body mass (LBM).

LBM (predominantly comprised of skeletal muscle) has several important functions.

- primary site of glucose disposal (with lower skeletal muscle mass contributing to poorer glycaemic control
- a strong determinant of resting metabolic rate; and thus loss of skeletal muscle with weight loss may predispose individuals to a greater chance of weight regain

Table 1. Definitions of Body Composition Compartments

Fat mass	Mass of all adipose tissue
Fat free mass	Fat free mass is total body mass minus total fat mass
Lean body mass	Lean body mass is fat free mass minus total bone mass
Skeletal muscle mass	Skeletal muscle mass is lean body mass minus connective tissue, skin, and other organs
Total body water	The summation of intra- and extra-cellular water

Body composition measurement

- Direct methods: (highest accuracy ↔ expensive)
  - computed tomography (CT)
  - magnetic resonance imaging (MRI)
- Indirect methods: (estimate body composition indirectly)
  - bioelectrical impedance analysis (BIA)
  - air displacement plethysmography (ADP)
  - dual-energy X-ray absorptiometry (DXA)

TABLE 1 | Advantages and disadvantages of imaging modalities in assessing myosteatosis.

	Advantages	Disadvantages
Computed tomography (CT)	• Differentiates SAT and IMAT • Axial and appendicular anatomic sites can be scanned • Excellent reproducibility and reliability of muscle and adipose tissue attenuation • Allows 3D reconstruction	• Cannot directly measure the location of fat storage or lipid droplets within muscle • High cost • Limited access • Ionizing radiation • Not portable
Peripheral quantitative computed tomography (pQCT)	• Differentiates SAT from intramuscular adipose and IMAT • Quantifies muscle density • Lower cost • Limited ionizing radiation • Portable device	• Axial and proximal appendicular anatomic sites cannot be scanned • Individual muscle groups cannot be segmented • Cannot distinguish between intramuscular fat and IMAT
Magnetic resonance imaging (MRI)	• Muscle compartments can be segmented • Differentiates SAT, intramuscular adipose, and IMAT • High quality visualization of IMAT distribution • Spectroscopy permits IMCL quantification	• Cannot measure muscle density • High cost • Limited access • Not portable • Cannot be used in individuals with metal implants • Lack of standardized protocols for scan acquisition and adipose tissue quantification
Quantitative ultrasound (QUS)	• Reliable measures of muscle thickness and echogenicity • Axial and appendicular anatomic sites can be scanned • Lower cost • No ionizing radiation • Portable device	• Inter-machine validity unknown • Consistency relies on probe placement, pressure, and angle of incidence • Cannot distinguish between intramuscular fat and IMAT

DXA, a two-compartment method of body composition analysis that separates body components into fat mass and fat-free mass, is one of the most popular and widely used non-invasive techniques for estimating whole-body and regional body composition [29]. When used in relation to body composition, the term ‘lean mass’ usually refers to muscle mass; however, lean mass comprises the combined weight of internal organs, muscle, connective tissue and water. It is important to consider the influence of these non-muscle components in DXA measurements of lean mass, and particularly the inability of DXA to calculate variable amounts of water [29], making it difficult to distinguish between loss of muscle and reduction in extracellular volume.

appendicular lean mass (a good marker of skeletal muscle mass)

Thus, the caloric loss from glucosuria, and not fluid loss, was responsible for the reductions [38]. This is supported by results from a small study finding that changes in extracellular water volume with SGLT-2is are transient, and not responsible for long-term weight loss with this drug class.

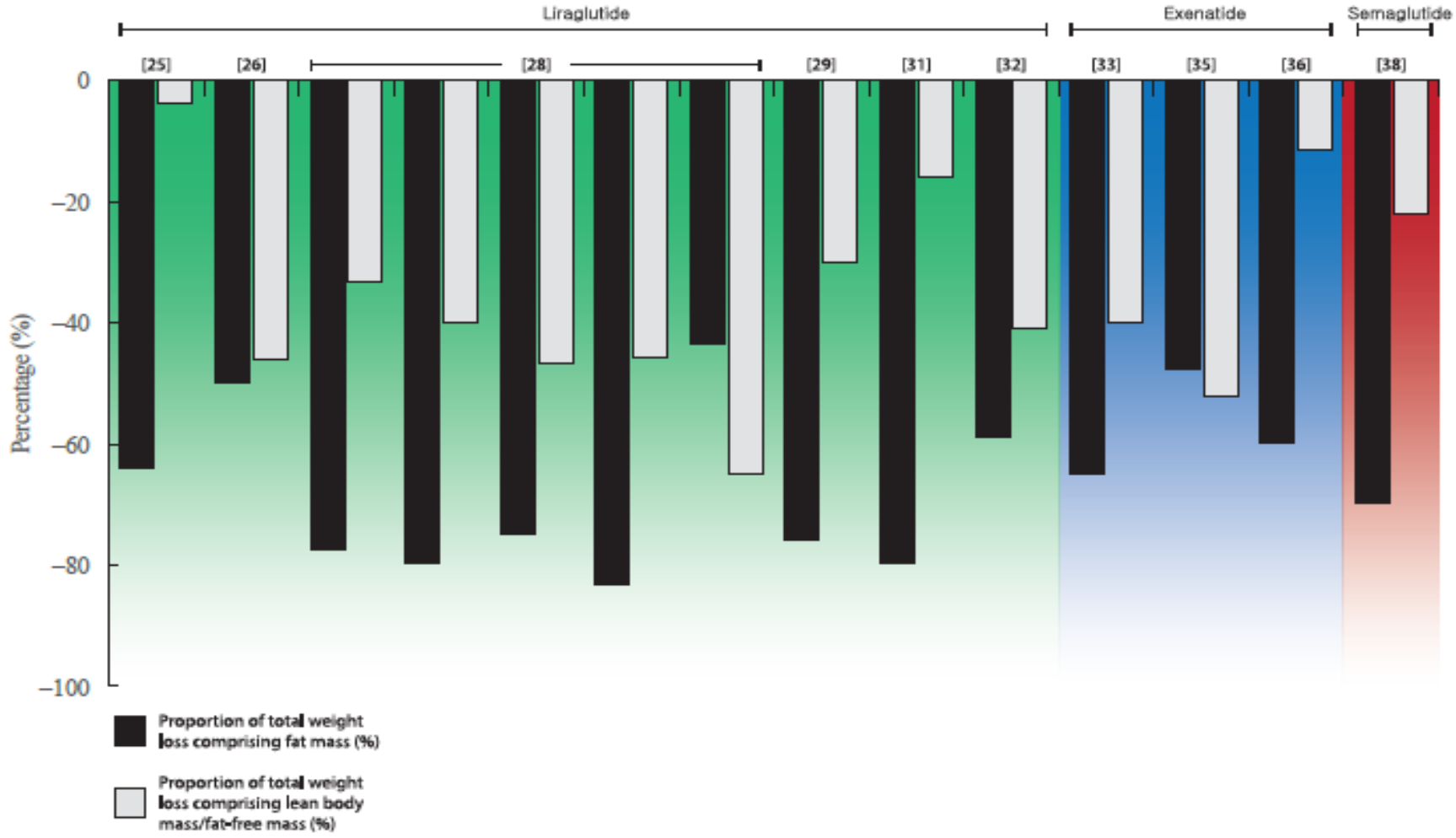


Fig. 1. Relative proportions of fat mass and lean body/fat-free mass within total weight loss elicited by glucagon-like peptide-1 receptor agonist therapy [25,26,28,29,31-33,35,36,38].

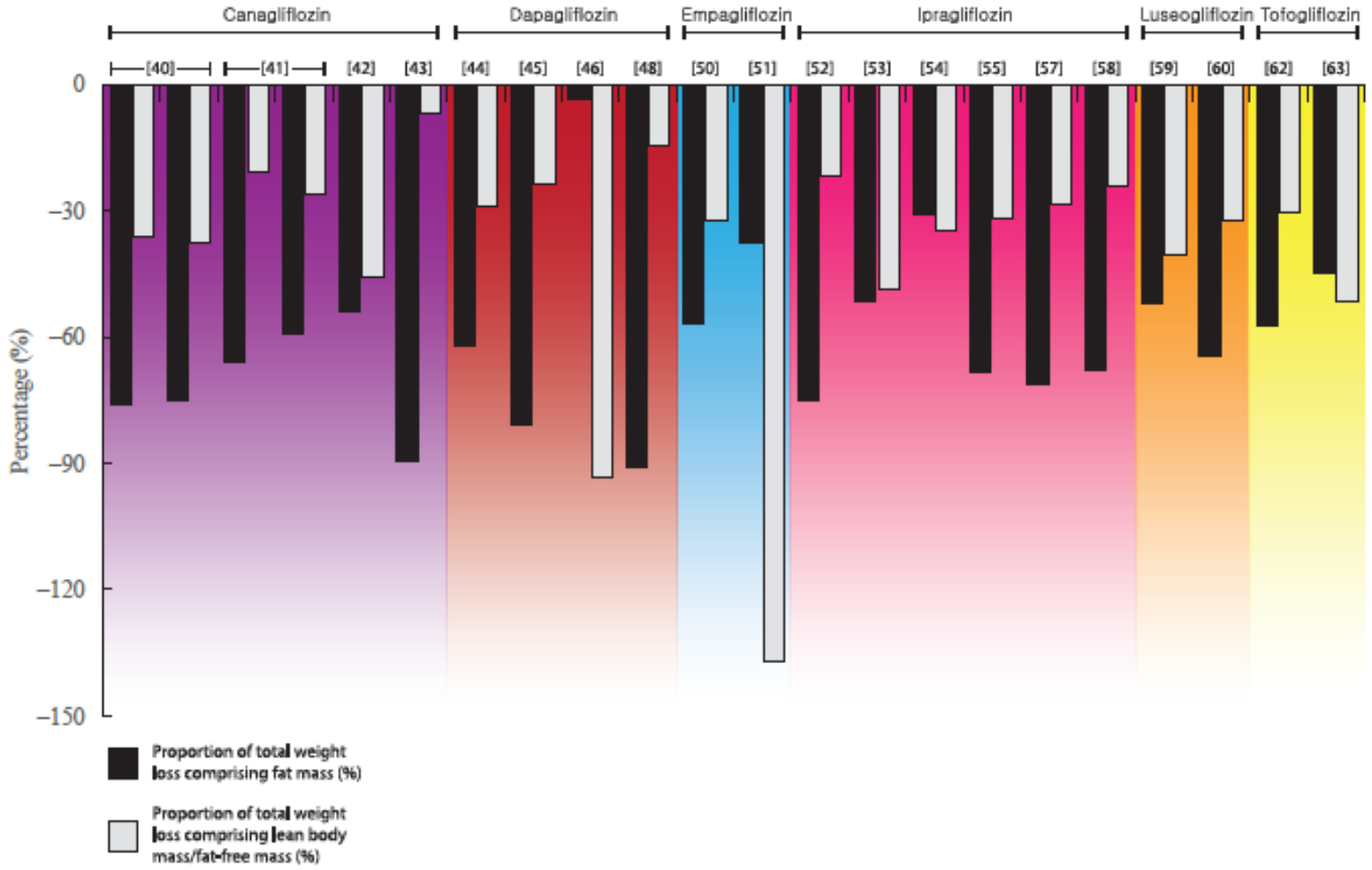


Fig. 2. Relative proportions of fat mass and lean body/fat-free mass within total weight loss elicited by sodium-glucose cotransporter 2 inhibitor therapy [40-46,48,50-55,57-60,62,63].

- Studies suggest muscle loss with these medications (as indicated by decreases in fat-free mass [FFM]) ranges from 25% to 39% of the total weight lost over 36–72 weeks.

- This substantial muscle loss can be largely attributed to the magnitude of weight loss, rather than by an independent effect of GLP-1 receptor agonists.

non-pharmacological caloric restriction studies with smaller magnitudes of weight loss result in 10–30% FFM losses.

age-related muscle loss (0·8% per year based on 8% muscle loss per decade from ages 40–70 years

GLP1 several times!

- It is hypothesised that substantial decreases in FFM due to short-term weight loss do not impact physical function,2 such as muscle strength.

It is possible that, despite the reduction in total muscle mass, muscle composition might improve, thereby enhancing muscle quality

muscle quality refers to the ratio of muscle strength to muscle mass .

The hypothesis of improving muscle composition with decreasing muscle mass should be explored in future research.

In addition to being a functional organ, muscle plays crucial metabolic roles that extend far beyond movement and strength

- Additionally, patients receiving GLP-1 receptor agonists are at increased risk for multiple factors contributing to muscle loss and sarcopenia, including metabolic dysfunction, inflammation, poor dietary intake, low physical activity, and comorbidities. The marked weight loss induced by these medications could therefore further exacerbate these risks.
-

Conclusion:

There are no data to establish whether treatment with GLP-1 receptor agonists is associated with physical frailty or sarcopenia. These effects would require long-term studies, which are not yet available, and the studies conducted to date were not designed to answer these questions.

Summary and Conclusions

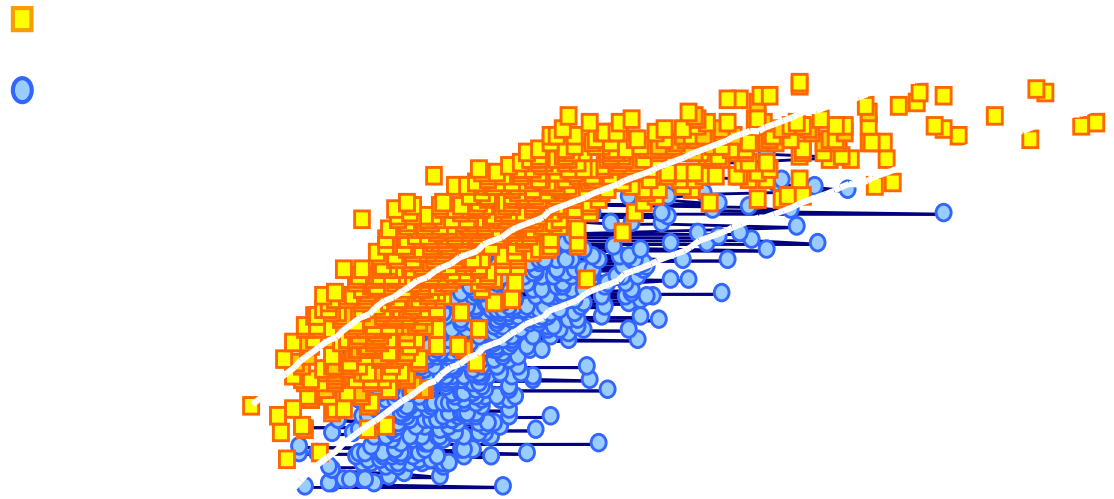
1) persons with obesity have more muscle mass than those with normal weight but poor muscle quality;

2) weight loss reduces muscle mass without adversely affecting muscle strength and improves global physical function, most likely because of reduced fat mass;
3) adding exercise (endurance and resistance type) to a hypocaloric diet helps preserve muscle mass during weight loss, and resistance-type exercise also improves muscle strength;

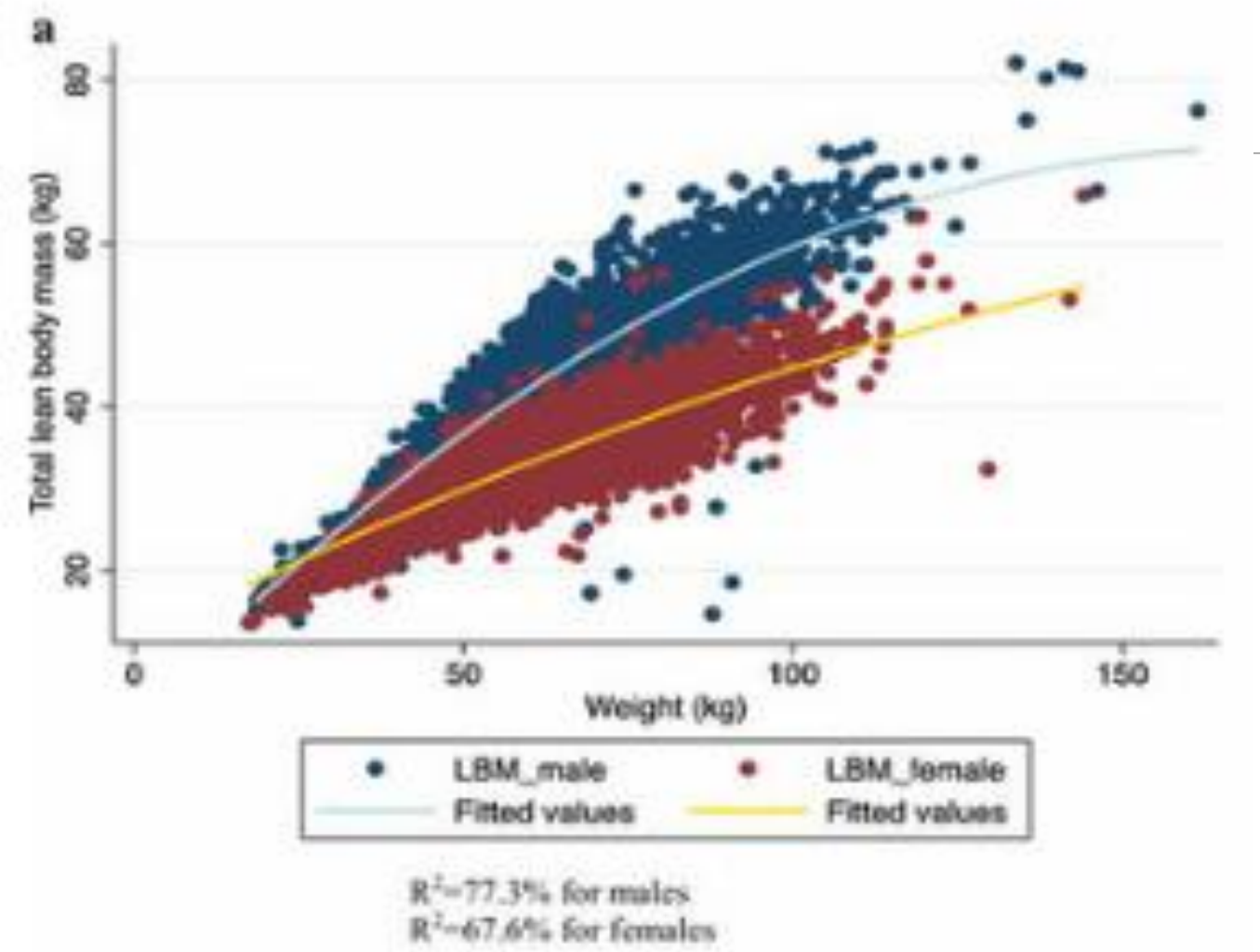
4) high protein intake helps preserve lean body and muscle mass but does not improve muscle strength and could have adverse effects on metabolic function.

Improving muscle quality, rather than preserving or increasing muscle mass, should therefore be the primary focus of therapeutic strategies for people with obesity.

Relationship Between BMI and Percent Body Fat in Men and Women



Adapted from: Gallagher et al. *Am J Clin Nutr* 2000;72:694.


a
Total lean body mass (kg)
20
40
60
80
0
50
100
150
Weight (kg)
LBM_male
Fitted values
LBM_female
Fitted values
R²=77.3% for males
R²=67.6% for females

Fat-free mass loss during weight loss

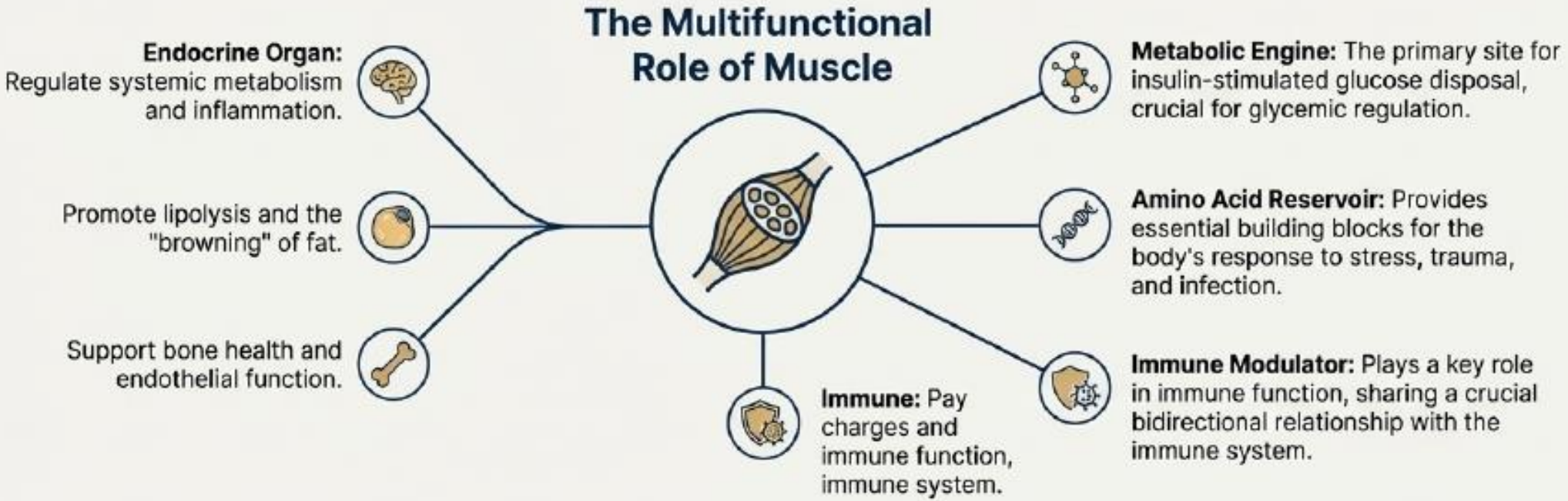
In persons with <u>normal weight</u>, the contribution of fat-free mass loss often exceeds 35% of total weight loss

In persons who are <u>overweight or obese</u>, fat-free mass contributes only ~20–30% to total weight loss, and weight regain does not prevent fat-free mass regain.

Fat-free mass loss: Men > women

Muscle Matters Far Beyond Movement

Skeletal muscle is a critical metabolic and endocrine organ. Its health is central to systemic well-being.



Clinical Implication: Substantial loss of high-quality muscle isn't just a loss of strength; it's a loss of metabolic and immune resilience.

Skeletal muscle importance

Muscle as a structural/functional organ

Risk of sarcopenia (defined as low muscle mass and impaired muscle function), especially in vulnerable populations, such as postmenopausal women and older adults.

Drug-induced weight loss without concurrent strategies to prevent substantial muscle loss can lead to, or exacerbate, sarcopenic obesity across the lifespan.

Sarcopenic obesity is prevalent and linked to poor health outcomes, such as increased risk of cardiovascular disease and higher morality rates.

Physical impairment and disability, poor quality of life, and shorter survival

Main tissue responsible for insulin-stimulated glucose disposal, and impaired uptake is common in obesity and has substantial effects on whole-body glucose turnover.

MUSCLE MASS VERSUS LEAN MASS AND GLP-1–BASED THERAPIES