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POTENTIAL COMPLICATIONS OF COMBINED THERAPIES ACCELERATED LEAN MASS LOSS

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TORONTO2026

The Future of Obesity Management:
From Weight Loss to Health Gain



ifso2026.org

Disclosures

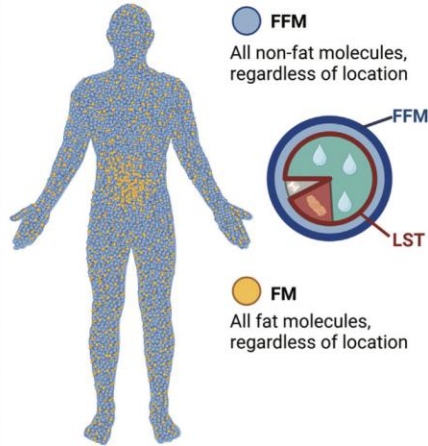
- **Speaker: Novo Nordisk, Merck, Medtronic, Johnson & Johnson MedTech**
- **Research support / grants: Medtronic, Marlex**

Expected loss $\neq$ Muscle failure

- Lean mass decreases with all effective weight-loss strategies.
- The proportion lost with incretin therapy is broadly comparable to lifestyle-induced weight loss.
- It becomes clinically concerning when loss is disproportionate, progressive, or accompanied by declining strength, function, or nutritional reserve.

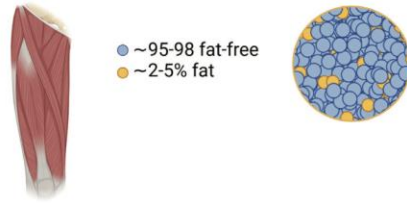
Lean mass is not synonymous with skeletal muscle

MOLECULAR LEVEL

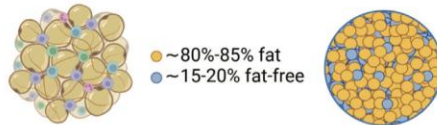


TISSUE/ORGAN LEVEL

SKELETAL MUSCLE



ADIPOSE TISSUE



Measured by DXA, BIA, BIS, ADP, UWW, 3DO, SKF, anthropometric equations

Measured by MRI, CT, US

Lean mass: water, protein, minerals, glycogen, organs, bone, and skeletal muscle.

1 kg of DXA-derived lean-mass loss cannot automatically be interpreted as 1 kg of lost skeletal muscle

Lean Mass Changes With Incretin Therapy Versus Lifestyle Intervention: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Naseem Eisa¹  | Omar Barood²

Diabetes, Obesity and Metabolism, 2026

Lean-mass loss is not disproportionate with incretin therapy

TABLE 2 | Body composition outcomes by intervention type.

Intervention	Studies (N)	Lean mass loss (kg)	Lean mass (%)	Fat mass loss (kg)
Semaglutide	7	−3.4 (−4.2 to −2.6)	35.2% (31.5–38.9)	−8.6 (−10.1 to −7.1)
Tirzepatide	5	−4.8 (−5.9 to −3.7)	25.4% (22.8–28.0)	−11.8 (−13.5 to −10.1)
Liraglutide	3	−2.8 (−3.9 to −1.7)	26.8% (23.1–30.5)	−6.8 (−8.2 to −5.4)
Lifestyle interventions	5	−2.4 (−3.2 to −1.6)	26.2% (24.1–28.3)	−5.9 (−7.1 to −4.7)
Lifestyle + resistance training	2	−1.2 (−1.8 to −0.6)	17.5% (14.2–20.8)	−5.6 (−6.8 to −4.4)
Overall	20	−3.2 (−3.9 to −2.5)	26.5% (24.2–28.8)	−7.9 (−9.2 to −6.6)

- Incretin agonists: 29.8% of weight loss from lean mass
- Lifestyle intervention: 26.2% — no significant difference ($p=0.42$)
- Lifestyle + resistance training: 17.5% — the most favorable profile

STEP UP: lean tissue decreased while chair-stand performance remained stable

- *MRI substudy: 55 participants, with semaglutide doses pooled (n=49) and placebo (n=6).*
- *Semaglutide produced 84.5% of weight loss from adipose tissue and 15.5% from lean tissue. The adipose-to-lean tissue ratio improved from 1.80 to 1.35.*
- *Change in the 30-second sit-to-stand test did not differ from placebo: ETD -0.1 repetition (95% CI -3.6 to 3.4; p=0.97).*
- *Interpretation: function remained stable, but pooled doses and only six placebo participants limit precision.*

Muscle quantity and function after bariatric surgery

SYSTEMATIC REVIEW AND META-ANALYSIS, 2026

64 studies

Absolute muscle quantity decreased after surgery.
Relative muscle mass generally increased.

Chair-stand performance and overall physical performance generally improved.

Absolute limb strength declined modestly or remained stable.

PROSPECTIVE RYGB COHORT

47 adults followed for 12 months

-13%

total lean mass

-9%

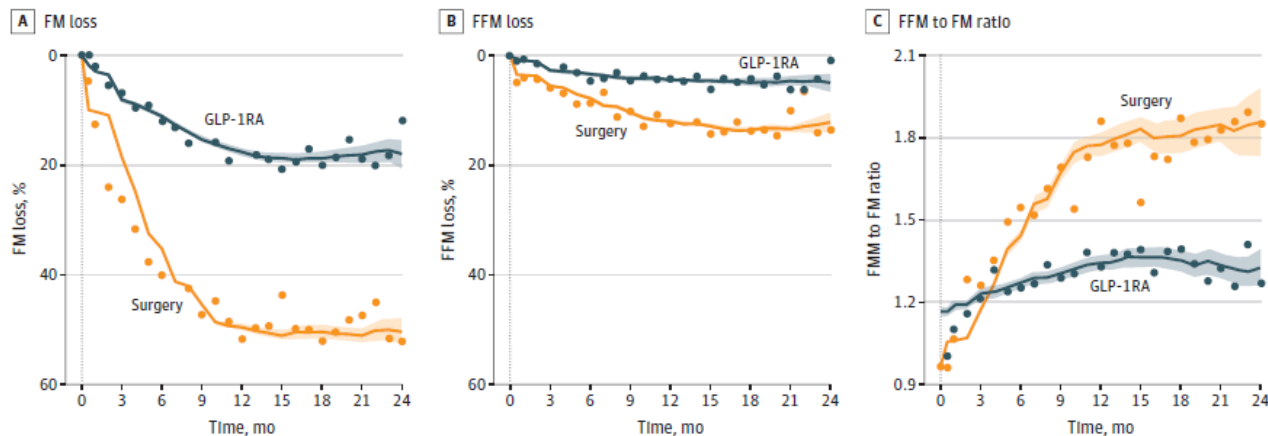
absolute grip strength

+32%

grip strength relative to BMI

Performance improved

Greater weight loss produces greater absolute FFM loss



Real-world cohort

Bariatric surgery: n=1,257

Semaglutide or tirzepatide:
n=1,809

Serial BIA over 24 months

At 12 months: FFM -10.6% after surgery vs -3.0% with GLP-1RA treatment. Fat mass fell much more, and the FFM/FM ratio improved in both groups.

Muscle health is defined by quality and function — not mass alone

- Obesity may increase absolute muscle mass while reducing strength relative to body size.
- Intentional weight loss can reduce lean mass while improving insulin sensitivity and muscle quality.
- 20% of RCTs have assessed body composition, while fewer than 5% have evaluated physical performance.

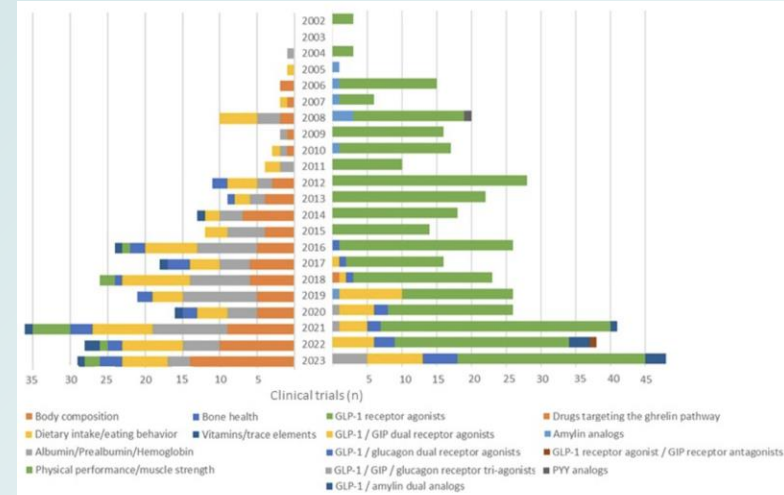
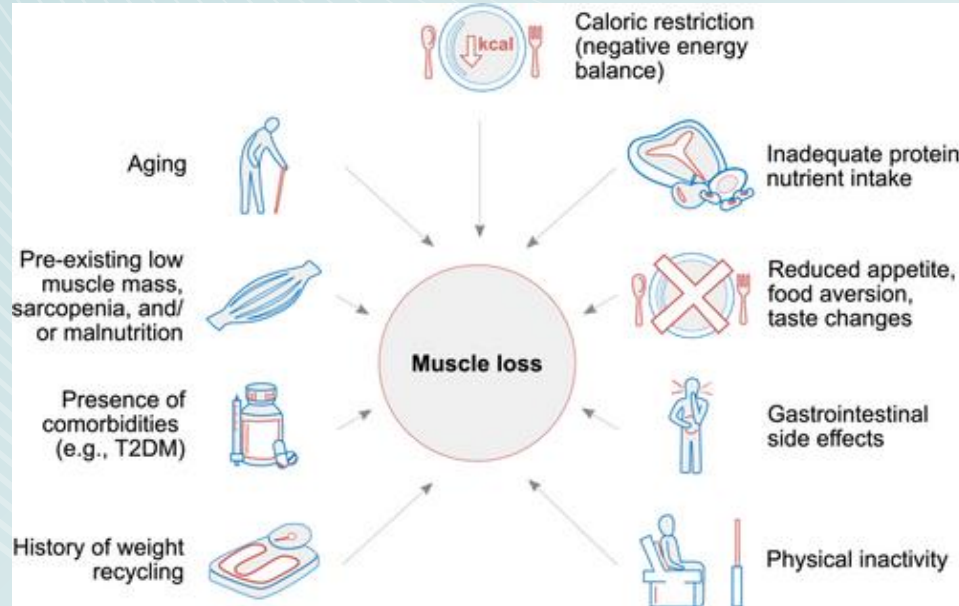


FIGURE 2 Temporal trend of RCTs by type of nutrient-stimulated hormone-based therapy and type of nutritional and functional outcomes.

Risk is concentrated in vulnerable phenotypes



Measure the patient — not only the compartment

TABLE 1 Characteristics of selected methods for assessing body composition in outpatient settings.^a

	Availability	Accuracy	Diagnostic performance	Longitudinal performance	Cost
MRI	●	●	●	●	●
Ct	●	●	●	●	●
DXa	●	●	●	●	●
ADP	●	●	●	●	●
Ultrasound	●	●	●	●	●
BiA	●	●	●	●	●
Anthropometry ^b	●	●	●	●	●

Muscle strength

Handgrip strength Knee flexion/extension



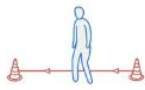
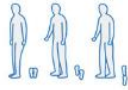
Physical performance

Timed-up-and-go

Sit-to-stand test

Balance test

Gait speed



- Start with the clinical trajectory: rate of weight loss, dietary intake, symptoms, mobility, and comorbid disease
- In higher-risk patients, measure body composition with the same method over time, under similar hydration conditions and add a simple functional measure

Mechanick et al. Obes Rev. 2025; Cruz-Jentoft et al. Age Ageing. 2019

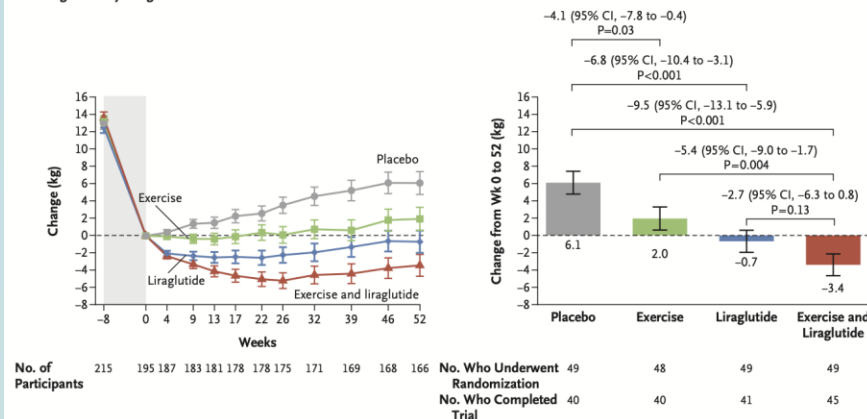
Clinical red flags

- **Loss exceeds the expected trajectory for the magnitude of weight loss.**
- **Handgrip, chair-stand, gait speed, mobility, or daily function deteriorates.**
- **Protein and energy targets cannot be maintained.**
- **Loss is progressive despite weight stabilization.**
- **A high-risk patient crosses a low-muscle or low-strength threshold.**

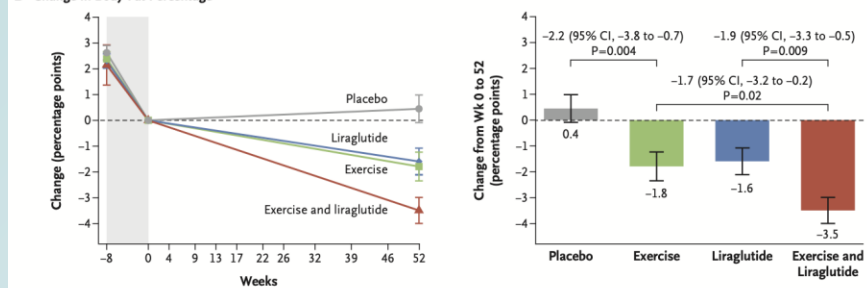
ORIGINAL ARTICLE

Healthy Weight Loss Maintenance with Exercise, Liraglutide, or Both Combined

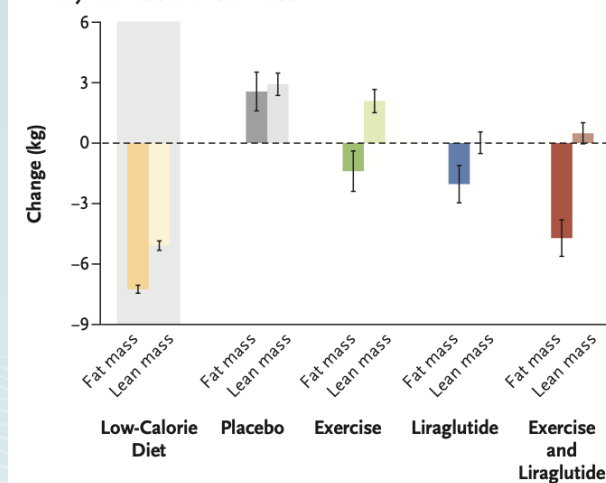
A Change in Body Weight



B Change in Body-Fat Percentage



A Body Fat Mass and Lean Mass



195 pts

13,1 kg diet-induced initial weight loss

In the S-LiTE trial, exercise added to liraglutide reduced the proportion of weight loss from lean mass: 12% with the combination vs 26% with liraglutide alone. Exercise also supported long-term weight maintenance.



Bimagrumb plus semaglutide alone or in combination for the treatment of obesity: a randomized phase 2 trial

Peer-reviewed phase 2 trial · 2026

Steven B. Heymsfield¹, Louis J. Aronne², Penelope Montgomery³, Lloyd B. Klickstein⁴, Laura A. Coleman⁵, Kiran Dole⁵, Linda Mindeholm⁶, Susan Spruill⁷, Xingyuan Li⁵, Kenneth M. Attie⁵ & for the BELIEVE trial investigators*

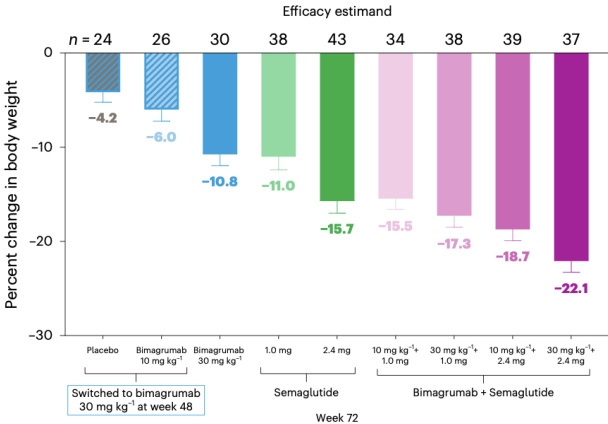
Activin type II receptor antibody
507 adults with obesity

Semaglutide 2.4 mg: 75.6% weight loss due to fat mass

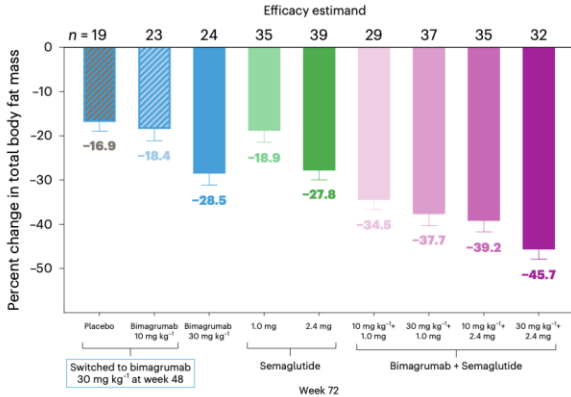
Bimagrumb alone: 100% weight loss due to fat mass

High-dose combination: 22.1% weight loss (92.2% coming from fat mass)

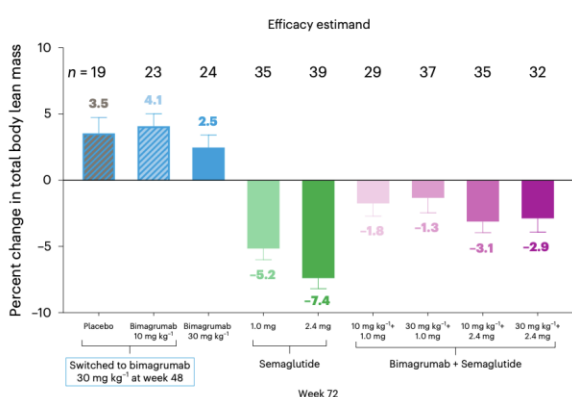
a Percent change in body weight



c Percent change in total body fat mass



d Percent change in total body lean mass



The pipeline is promising — clinical benefit is not yet proven

- *EMBRAZE: apitegromab + tirzepatide preserved 54.9% of lean mass lost versus tirzepatide alone at 24 weeks.*
- *COURAGE: trevogrumab ± garetosmab preserved up to 80% of semaglutide-associated lean-mass loss in interim analyses.*

Both programs reported favorable fat-to-lean loss ratios.

These are phase 2, investigational results; durability, safety, strength, function, and patient-centered benefit remain the decisive endpoints.

Take-home messages

- Expected lean-mass loss does not necessarily mean muscle loss or impaired muscle quality.
- Concern begins with vulnerability, disproportionate loss, or declining strength and function.
- Assess risk before combining surgery and potent pharmacotherapy.
- Protein optimization and resistance training are current standard care; muscle-targeted drugs remain investigational.



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“Advancing Multimodal Obesity Care”

24–27 August 2027

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See you in

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Thank you
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