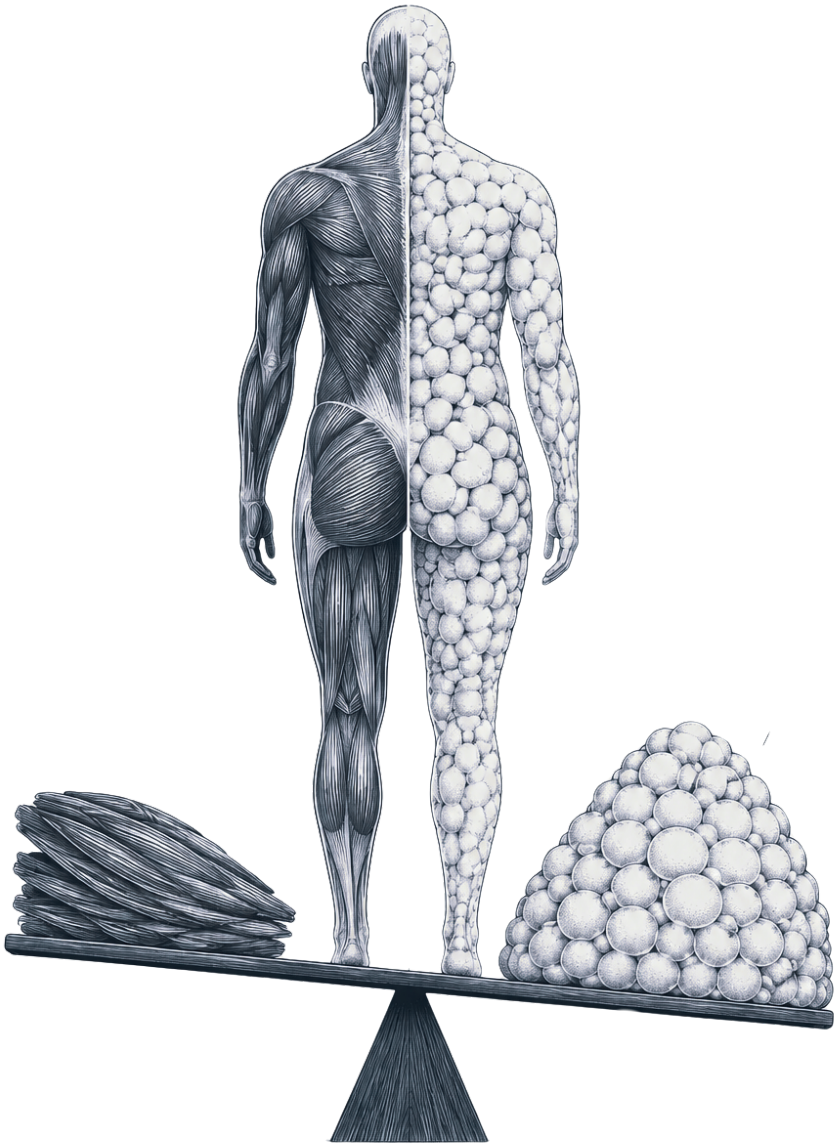
The Raven Brief

The Lean Mass Problem: What the GLP-1 Conversation Is Missing



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Why I'm Writing This

GLP-1 medications — semaglutide (Ozempic, Wegovy), tirzepatide (Mounjaro, Zepbound), liraglutide (Victoza, Saxenda) — have become the most widely prescribed weight management drugs in modern medicine. They produce real, measurable weight loss. They improve blood sugar. They reduce cardiovascular events in patients with established heart disease. The data on these endpoints is genuine, and I'm not writing to dispute it.

I'm writing about something else. Something the published trials make clear but that prescribing practice has not yet caught up with: a substantial fraction of the weight people lose… is lean mass, not fat; and lean mass includes, but is not limited to, skeletal muscle. And in the patient populations these drugs are now being recommended for first — older adults, those with heart failure, those with cardiovascular disease, those with chronic kidney disease — preservation of muscle and functional reserve becomes especially important.

This is not a fringe concern. The numbers come from the manufacturers' own registration trials. They are published in major cardiology and metabolism journals. They are documented well enough that the field's leading reviews now openly debate whether the muscle loss is acceptable, dangerous, or somewhere in between.

What I want to do in this brief is lay out what the data actually says, why it matters clinically, and what comprehensive metabolic care should look like alongside — or instead of — this medication class.

What the Trials Actually Show

In the STEP 1 trial of semaglutide for weight management, patients lost an average of 15.2 kg (~33.5 lbs) over 68 weeks. In the DXA substudy of 140 participants, total lean body mass decreased by approximately 9.7%, accounting for roughly 39% of the weight lost. While the proportion of lean mass relative to total body mass actually improved slightly, the absolute reduction in lean tissue is clinically meaningful, particularly in patients with limited muscle reserve.[1]

In the SURMOUNT-1 trial of tirzepatide, body composition analyses reported approximately 25% of weight lost as lean mass — a proportion similar to that observed with placebo, suggesting a pattern of weight loss consistent with non-pharmacologic weight reduction.[2]

In trials of liraglutide, lean mass loss has been reported as a substantial component of total weight reduction, though specific proportions vary considerably across studies and analytic methods.[3]

For comparison, diet-and exercise-induced weight loss is typically associated with about 25% fat-free mass loss—the "quarter fat-free mass rule."[4]
In GLP-1 trials, that proportion is often comparable or higher, and in some cases markedly higher—indicating that a larger share of the weight lost may come from lean tissue.

The 2025 SEMALEAN study, which followed 115 patients on semaglutide for twelve months and measured body composition with DXA scans, observed significant fat mass reduction with an early decline in lean mass that stabilized over time, alongside improvements in muscle function. Notably, the proportion of patients meeting criteria for sarcopenic obesity decreased over the study period.[5]

Lean mass loss during GLP-1–associated weight reduction is well-documented; the clinical significance and long-term impact remain actively debated.

Why This Matters Clinically

Lean body mass is not cosmetic. It is the largest reservoir of metabolically active tissue in the body. It plays a central role in resting energy expenditure and is a primary site of glucose disposal, with greater muscle mass consistently associated with improved insulin sensitivity. It underpins functional capacity, helping reduce the risk of falls and fractures in older adults, and is strongly associated with survival across conditions including cardiovascular disease, cancer, and chronic kidney disease.

When a patient loses substantial lean mass, several downstream effects may occur:

- Resting metabolic rate typically declines, meaning fewer calories are required to maintain the same weight. Following discontinuation of therapy, this reduction in energy expenditure may contribute to weight regain relative to baseline.[6]
- Improvements in insulin sensitivity may also be less robust than they would be if a greater proportion of the weight loss were adipose tissue, potentially overstating the metabolic benefit.
- Loss of lean mass is also associated with reduced strength and functional capacity, which can increase the risk of falls and fractures, particularly if bone density is concurrently declining.
- In patients with existing cardiovascular disease or heart failure, reductions in overall lean mass may reflect decreased physiologic reserve, which can be clinically relevant in the setting of acute stress or recovery.

These are not theoretical concerns—they reflect known physiologic consequences of disproportionate lean mass loss during weight reduction.

The Bone Density Question

Lean mass loss during weight reduction does not occur in isolation. Bone density appears to follow a similar pattern—declining in the absence of adequate mechanical loading and preserved when that stimulus is maintained.

In a randomized trial comparing exercise alone, GLP-1 receptor agonist therapy alone, and the combination of both, reductions in bone mineral density at the hip and lumbar spine were observed in the medication-only group, while bone density was preserved in groups that included structured exercise.[7]

These findings suggest that pharmacologic weight loss without concurrent resistance training may place bone health at risk, whereas the addition of mechanical loading can mitigate that effect.

This distinction has not yet been consistently reflected in routine prescribing practice. Patients started on these medications are not typically given structured resistance training protocols, monitored for protein adequacy, or followed with serial assessment of bone density or body composition.

The implication is not that GLP-1 receptor agonists inherently degrade bone, but that their effects on body composition—when implemented in isolation—may create conditions under which both lean mass and bone density decline.

For a postmenopausal woman with osteopenia, this may not be a neutral intervention. Estrogen decline already shifts the balance toward bone resorption; layering pharmacologic weight loss without adequate mechanical loading may further accelerate that trajectory. Over time, this may increase fracture risk in a population already vulnerable to it. Hip fractures in older women carry a one-year mortality rate estimated between 20% and 30%.[8]

The Cardiovascular Paradox

The 2026 American Diabetes Association Standards of Care increasingly prioritize GLP-1 receptor agonists and related therapies for patients with type 2 diabetes and specific comorbidities, including established cardiovascular disease, heart failure with preserved ejection fraction, chronic kidney disease, and metabolic dysfunction–associated steatohepatitis.[9]

These recommendations are grounded in consistent evidence demonstrating improvements in glycemic control, weight reduction, and cardiovascular risk.

At the same time, these are also the patient populations in whom preservation of lean mass is most clinically important.

Patients with heart failure are at risk for cardiac cachexia, a syndrome characterized by unintentional weight loss and muscle wasting that carries an independent association with mortality. Emerging literature suggests that while GLP-1–based therapies improve cardiovascular outcomes, their effects on body composition may be relevant in patients already vulnerable to muscle loss.[10]

Similarly, in patients with chronic kidney disease, reductions in muscle mass are associated with poorer functional status and worse clinical outcomes. In older adults and those with established cardiovascular disease, loss of lean mass is associated with reduced physiologic reserve and diminished recovery capacity following acute illness or injury.

This creates a clinical tension: a therapy that improves cardiovascular endpoints while simultaneously altering body composition in ways that may carry risk for certain patients.

The literature has not yet fully resolved this tension. Some analyses suggest that lean mass loss during weight reduction is proportionate and may represent an adaptive response. Others argue that the long-term consequences—particularly in vulnerable populations—remain insufficiently studied.[11] [12]

What is clear is that these therapies are not compositionally neutral. The clinical question is not whether they work—they do—but how they are implemented, in whom, and with what protective strategies in place.

What Should Happen Instead

For many patients—particularly women with hypothyroidism or Hashimoto's—the issue is not a lack of effort. They've adjusted their diet. They've tried to exercise. They've followed medical advice. And despite that, the weight either does not move, or it returns just as quickly.

In that context, GLP-1–based therapies can feel less like an option and more like the only path forward. This is not an argument against their use. It is an argument against using them in isolation.

Weight loss, particularly in the setting of thyroid dysfunction, is not simply a matter of caloric balance. The composition of that weight loss—and its impact on long-term metabolic function—matters. A patient with hypothyroidism who loses weight at the expense of lean mass may find that her metabolic rate declines further, making long-term weight maintenance even more difficult once the medication is stopped.

A more complete approach to care must therefore include strategies designed not only to produce weight loss, but to preserve lean mass, maintain bone density, and support metabolic stability over time.

This begins with identifying the dominant drivers of dysfunction. In many thyroid patients, persistent symptoms and weight resistance are not explained by thyroid labs alone. Interactions between the thyroid (HPT axis), adrenal regulation (HPA axis), and reproductive hormones (HPG axis) often shape the clinical picture. Treating thyroid numbers in isolation does not resolve that system-level dysfunction.

It also requires resistance training as a foundational component of care—not as an optional recommendation, but as a primary intervention. Skeletal muscle plays a central role in metabolic regulation, and preserving it during weight loss is critical. Adequate protein intake is equally important. In most patients, this falls in the range of 1.0 to 1.2 grams per kilogram of body weight per day, and in some cases higher depending on age, activity level, and clinical context.

When clinically appropriate, body composition and bone density should be monitored—particularly in patients at higher risk for sarcopenia, osteopenia, or long-standing metabolic dysfunction.

And this work requires continuity. Thyroid-driven metabolic dysfunction does not resolve through episodic intervention. It requires ongoing adjustment based on physiologic response over time.

A Clinical Decision Framework

For patients—and for the clinicians who care for them—the question is rarely "GLP-1 or no GLP-1."

The more relevant question is whether pharmacologic therapy is being used as a primary intervention, or as one component within a structured metabolic strategy.

In practice, this often comes down to two different clinical scenarios.

In the first, the patient presents with significant metabolic disease, limited physiologic reserve, or barriers that make sustained lifestyle intervention difficult. In this context, GLP-1–based therapy, when combined with appropriate nutritional support, resistance training, and clinical monitoring, may be the most effective path forward.

In the second, the patient is physiologically capable of engaging in structured metabolic intervention, but has not been given a program calibrated to her underlying drivers of dysfunction. In these cases, a comprehensive approach—targeting nutrition, resistance training, sleep, stress regulation, and hormonal context—may support meaningful and potentially more durable outcomes without immediate reliance on pharmacologic therapy.

These are not interchangeable patients. Treating them as such risks both underutilizing effective therapies in those who need them and overutilizing them in those who may not.

Regardless of the path chosen, certain principles remain constant: preservation of lean mass, maintenance of bone density, and support of long-term metabolic function should be considered core treatment objectives, not secondary considerations.

This requires asking different questions at the point of care:

What is the plan for preserving lean mass during weight loss?
What is the plan for maintaining or monitoring bone density?
How will body composition—not just body weight—be tracked over time?
What interventions are in place to support long-term metabolic stability after weight loss is achieved?

When these questions are addressed, treatment becomes more precise. When they are not, even effective therapies risk being applied in ways that do not fully serve the patient over time.

Bernadette Spencer is a board-certified Family Nurse Practitioner and the founder of Raven Metabolic & Hormone Health, a virtual functional medicine practice serving women across New York State.

For referring providers: "If you have a patient with hypothyroidism or Hashimoto's who has been unable to achieve or maintain weight loss despite appropriate thyroid management and lifestyle modification, Raven MHH offers comprehensive metabolic assessment and structured intervention designed to address the underlying drivers of resistance.

F**or patients:** "If you've been doing the work—adjusting your diet, staying active, following your doctor's recommendations—and still not seeing results, the issue may not be effort. It may be that the approach hasn't addressed the full picture of what's driving your metabolism."

References

Note on references:

This brief draws on a focused selection of peer-reviewed evidence relevant to clinical decision-making as of May 2026. The literature on GLP-1 therapies and body composition continues to evolve. Where specific trial data are cited (e.g., STEP 1, SURMOUNT-1, SEMALEAN), figures are drawn from published results and supporting review literature that synthesize these findings.

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