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Dietary Protein as an Adjunct to GLP-1–Based Obesity Pharmacotherapy to Preserve Lean Body Mass

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Abstract*—Glucagon-like peptide-1 (GLP-1) receptor agonists and dual incretin agonists have transformed obesity management, producing weight loss previously achievable only through bariatric surgery. However, a substantial proportion of this weight loss is le an body mass, prompting intense interest in strategies to preserve skeletal muscle during pharmacotherapy. Structured exercise has advanced from a general lifestyle recommendation to an evidence-based therapeutic partner of incretin therapy, a relationship now described as the "metabolic alliance." Randomised trials have validated exercise as a co-therapy that improves body composition, physical function, cardiorespiratory fitness, bone health, and long-term weight-loss maintenance. In contrast, dietary protein—an equally plausible contributor to muscle preservation—has received far less direct clinical study during GLP-1-based treatment, with current recommendations largely extrapolated from calorie-restriction, ageing, and sports-nutrition research. This discussion paper argues that exercise and protein are complementary rather than competing interventions: exercise supplies the anabolic stimulus, whereas protein supplies the amino-acid substrate for muscle protein synthesis. We outline priority research questions and contend that the metabolic alliance should be broadened into a metabolic–nutritional alliance, in which nutrition is investigated with the same rigour recently applied to structured exercise*.

***Keywords*—** *Obesity; GLP-1 receptor agonists; tirzepatide; semaglutide; lean mass; skeletal muscle; dietary protein; resistance exercise; weight-loss maintenance; metabolic alliance*.

I. INTRODUCTION

The emergence of glucagon-like peptide-1 (GLP-1) receptor agonists and dual incretin agonists has transformed obesity management, achieving levels of weight reduction previously attainable only through bariatric surgery [1–3]. However, alongside these remarkable metabolic benefits, concerns have arisen regarding the loss of lean body mass accompanying rapid pharmacologically induced weight loss.

In response, recent clinical investigations have increasingly focused on strategies to preserve skeletal muscle during obesity treatment. Structured exercise has consequently evolved from being viewed as a general lifestyle recommendation to an evidence-based therapeutic partner of obesity pharmacotherapy, culminating in the concept of a "metabolic alliance" [4,5].

While this conceptual evolution represents a major advance, an equally important component of muscle preservation has received comparatively less direct clinical investigation: dietary protein.

The Success of the Metabolic Alliance

Randomized studies evaluating structured exercise alongside incretin-based therapies have demonstrated improvements in body composition, physical function, cardiometabolic health, and long-term weight-loss maintenance [6–9]. Exercise has been recognized as a crucial supplement to drug treatment, thanks to these findings.

Importantly, the rationale for exercise extends beyond increasing energy expenditure. Exercise provides the mechanical and molecular stimulus required for muscle remodeling, enhances insulin sensitivity, improves mitochondrial function, preserves bone health, and maintains physical performance.

The evidence supporting exercise has therefore progressed from physiological plausibility to randomized clinical validation.

The Nutritional Evidence Gap

Unlike exercise, recommendations regarding protein intake during GLP-1 therapy remain largely extrapolated from studies involving calorie restriction, aging, sports nutrition, and non-pharmacological weight-loss interventions.

Most contemporary reviews recommend increasing protein intake during incretin therapy, often suggesting intakes exceeding conventional dietary recommendations [10]. Nevertheless, these recommendations are consistently accompanied by an important limitation: direct randomized evidence in patients receiving GLP-1-based pharmacotherapy remains sparse.

Consequently, nutritional guidance has advanced more rapidly than the clinical evidence supporting it.

Exercise and Protein Are Complementary

The current discussion should not be framed as exercise versus protein. Rather, these interventions address different components of muscle preservation. Exercise provides the anabolic stimulus through mechanical loading and activation of

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adaptive signaling pathways. Dietary protein supplies the amino acid substrate required for muscle protein synthesis and tissue repair. Preservation of skeletal muscle during substantial energy deficit is therefore unlikely to depend exclusively on either intervention. Instead, optimal outcomes may require both adequate anabolic stimulation and sufficient nutritional support. This physiological complementarity provides a compelling rationale for studying dietary protein with the same rigor that has recently been applied to structured exercise.

Priorities for Future Research

Several clinically relevant questions remain unanswered.

- Does increasing protein intake independently reduce lean mass loss during GLP-1-induced weight reduction?
- What daily protein intake best preserves muscle mass and function during pharmacotherapy?
- Does protein quality influence clinical outcomes?
- Are improvements in muscle function comparable to those achieved through exercise?
- Do structured exercise and high-protein nutrition exert additive or synergistic effects when combined?

Answering these questions will require adequately powered randomized trials comparing pharmacotherapy alone, pharmacotherapy combined with high-protein nutrition, pharmacotherapy combined with structured exercise, and pharmacotherapy incorporating both interventions. The recently registered LEAN-PREP trial exemplifies this four-arm design, randomising 232 adults with obesity initiating semaglutide or tirzepatide therapy (1:1:1:1) to control, resistance exercise, protein supplementation targeting 1.6 g/kg/day, or combined resistance exercise and protein, with MRI-measured quadriceps cross-sectional area as the primary outcome [11].

II. Conclusion

The concept of the metabolic alliance has appropriately highlighted the indispensable role of exercise in contemporary obesity pharmacotherapy. However, muscle preservation depends not only on mechanical stimulation but also on nutritional substrate.

Although higher protein intake is now widely recommended during incretin therapy, the supporting clinical evidence remains substantially less developed than that for exercise. Closing this evidence gap should become a research priority.

Future investigations should move beyond viewing exercise and nutrition as separate supportive measures and instead evaluate them as complementary biological interventions capable of maximizing the quality, functionality, and durability of pharmacologically induced weight loss. Such an approach may ultimately expand the current metabolic alliance into a broader metabolic–nutritional alliance.

Declarations

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