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Opinion

Preserving Lean Mass During GLP-1RA-Induced Weight Loss: The Potential Role of Ketogenic Metabolic Therapy in Improving Weight-Loss Quality

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Incretins and body composition

GLP-1 receptor agonists and dual GIP/GLP-1 agonists have changed obesity treatment remarkably quickly. Semaglutide and tirzepatide produce levels of weight reduction previously associated mainly with bariatric surgery, together with clear improvements in glycemic control and cardiovascular risk.[1-3] As their use expands, attention is moving beyond total body weight alone. The composition of that weight loss is becoming harder to ignore.

Weight reduction during incretin-based therapy does not occur exclusively in adipose tissue. Clinical studies consistently report concomitant declines in lean mass and fat-free mass.[1,4,5] In STEP 1, lean mass reduction accounted for roughly 39% of total weight loss with semaglutide [1]. A similar trend has been described in patients treated with tirzepatide.[4]

Interpreting these results is not straightforward. Lean mass measurements from DXA or bioimpedance analysis also include water, glycogen-associated fluid, connective tissue, and organ mass. MRI-based analyses suggest that part of the observed decline may reflect reduced intramuscular lipid accumulation and changes in muscle composition rather than overt muscle wasting.[6,7] Still, excessive reductions in metabolically active tissue may be problematic, particularly in older adults, postmenopausal women, and patients with sarcopenic obesity.[8]

Muscle mass during weight loss

Skeletal muscle influences far more than physical performance alone. Resting energy expenditure, glucose disposal, metabolic flexibility, and long-term weight stability are all closely linked to lean tissue preservation. This becomes particularly relevant once obesity is viewed as a chronic relapsing disease rather than a temporary condition treated through short-term caloric restriction.[9]

The Minnesota Starvation Experiment demonstrated that incomplete restoration of lean tissue after prolonged caloric restriction promotes persistent hyperphagia and preferential fat regain during refeeding.[10,11] Modern obesity pharmacotherapy obviously differs from starvation conditions, yet the physiological principle remains relevant. Weight regain after discontinuation of GLP-1RA therapy is frequently observed.[12] Whether reductions in lean tissue contribute to this process remains uncertain, but the question is legitimate.

The issue, then, is not only how much weight patients lose, but how that loss is distributed across body compartments.

Ketosis and protein turnover

Nutritional therapy becomes particularly important here because appetite suppression alone cannot determine the metabolic quality of weight loss. The caloric deficit may be pharmacologically induced, but protein turnover, substrate utilization, and nitrogen balance still depend heavily on nutritional composition.

Nutritional ketosis modifies metabolism in ways that are not entirely explained by carbohydrate restriction alone. Nutritional ketosis modifies fuel partitioning and increases circulating ketone bodies, particularly beta-hydroxybutyrate, which acts not only as an oxidative substrate but also as a signaling metabolite involved in inflammation, oxidative stress, and skeletal muscle metabolism.[13]

One of the most debated aspects of ketosis during caloric restriction is its potential protein-sparing effect. Reduced reliance on amino acids for gluconeogenesis may attenuate nitrogen losses and partially limit proteolysis.[14] Experimental human studies also suggest that beta-hydroxybutyrate may suppress skeletal muscle protein breakdown during catabolic stress.[15]

Human evidence in obesity treatment remains limited. Even so, the possibility that nutritional ketosis may attenuate lean tissue loss during prolonged caloric restriction appears physiologically coherent.

Appetite suppression and nutritional risk

GLP-1RAs reduce reward-driven eating behavior and decrease preference for highly palatable foods.[16,17] Nutritional ketosis often acts in the same direction. In some patients, this may facilitate adherence and simplify caloric restriction. In others, the overlap becomes more complicated clinically.

Reduced appetite can easily translate into inadequate protein intake, low dietary variety, gastrointestinal intolerance, and progressive reductions in lean tissue when nutritional supervision is insufficient. Some patients receiving incretin-based therapies report difficulty consuming adequate meals, especially during the early phases of treatment. Additional appetite suppression associated with ketosis may further reduce spontaneous food intake.

For this reason, ketogenic interventions during GLP-1RA treatment should not be viewed simply as a strategy to intensify anorectic effects. Protein adequacy, micronutrient intake, meal quality, and body composition monitoring remain central clinical issues.[17]

Clinical use of ketogenic interventions

Ketogenic therapy in obesity management is often simplistically described as a high-fat diet. Contemporary very low-calorie ketogenic interventions (VLCKD/VLEKT) differ substantially from this interpretation. These are structured medical protocols characterized by controlled carbohydrate restriction, adequate protein intake, micronutrient supplementation, and progressive dietary transitions [18, 19].

Their defining feature is the induction of clinically meaningful nutritional ketosis rather than extreme lipid consumption.

This distinction matters during pharmacological obesity treatment. Poorly formulated low-calorie diets, combined with incretin therapy, may unintentionally exacerbate reductions in protein intake and lean tissue. Structured ketogenic approaches with adequate protein provision and clinical supervision may instead favor a more selective reduction in adipose tissue.

Combining pharmacological and nutritional strategies

Ketogenic interventions have recently been evaluated in combination with incretin-based pharmacotherapy. Camajani et al. reported greater weight reduction when liraglutide was combined with a very low-calorie ketogenic diet compared with ketogenic therapy alone [20]. Schiavo et al. later observed better preservation of fat-free mass, muscle strength, and resting metabolic rate when tirzepatide was combined with low-energy ketogenic therapy compared with a conventional low-calorie dietary approach [21].

The available evidence is still preliminary. Even so, these observations suggest that body composition during pharmacological weight loss may be modifiable through nutritional strategy rather than determined by drug therapy alone.

Preserving skeletal muscle during caloric restriction is difficult without resistance exercise. Mechanical loading is among the most effective interventions currently available for preserving skeletal muscle during caloric restriction [22]. In patients receiving incretin-based therapies, resistance training may help maintain muscle protein synthesis, neuromuscular performance, and resting energy expenditure.[23]

Protein intake is equally important. Several authors support higher protein targets during obesity treatment, particularly in individuals at risk for sarcopenia.[24] Protein quality, leucine content, and meal distribution may all influence muscle protein synthesis during prolonged caloric restriction.[25] During GLP-1RA treatment, ketogenic interventions cannot rely on spontaneous food intake alone. Preserving lean tissue requires deliberate protein planning rather than further appetite suppression.

Competing Interests

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