

# GLP-1 receptor agonists induce loss of lean mass: so does caloric restriction

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## INTRODUCTION

The widespread prevalence of obesity and its adverse health effects have made sustained weight loss strategies a public health priority. While the causes of obesity are still debated,<sup>1</sup> it is well established that a chronic positive or negative energy balance results in weight gain or loss, respectively. Caloric restriction (CR) with optimal nutrition has the potential to reverse several obesity-related metabolic complications, such as type 2 diabetes mellitus (T2DM), hepatic steatosis and hypertension.<sup>2</sup> Challenges in implementing long-term CR regimens, such as low adherence, psychological impact and metabolic adaptation, have made the search for pharmacological alternatives an attractive area of research, though progresses in this field have, until recently, been limited.

## A new tool in the arsenal

The recent introduction of glucagon-like peptide-1 (GLP-1) receptor agonists (RA), a class of widely used drugs for the treatment of T2DM, as anti-obesity medication, is posed to revolutionise the management of obesity. Indeed, GLP-1 RA can achieve weight losses of about 15%–25% while being relatively well tolerated by the patients (for comparison, CR results in weight loss of about

10%–20% in 6 months, and metabolic surgery achieves ~25%–35%).<sup>3–6</sup> The primary mechanism of action of GLP-1 RA is through appetite suppression via its action at the level of the central nervous system and delayed gastric emptying, thus facilitating the adherence to a CR state. However, the significant weight loss associated with GLP-1 RA has raised concerns regarding its impact on lean body mass. The latter, in addition to have key structural roles (eg, balance, locomotion, respiration), has essential metabolic functions, such as hormones release (myokines) that are involved in inter-organ communication and postprandial glucose disposal, among other roles.<sup>7</sup>

CR studies show a trade-off in weight loss composition. While around 60% of weight loss comes from fat mass, approximately 30% comes from lean mass. This proportion fluctuates based on factors such as sex, age and the severity of calorie restriction (more severe CR leads to greater muscle loss), and dietary composition.<sup>8</sup> Even in very-low-calorie ketogenic diets (VLCKD), which are characterised by higher lean mass loss due to the severity of CR, the former can be mitigated when this dietary approach is combined with resistance training and strategic protein intake.<sup>9–10</sup> Pharmacologically induced weight loss with GLP-1 RA shows a lean mass loss of about 25%–40%,<sup>8</sup> which could be particularly concerning in specific populations, such as elderly or patients with sarcopenic obesity; the same, however, holds true for CR approaches in these musculoskeletal fragile populations. Nevertheless, clinical studies indicate that GLP-1 RA-induced weight loss leads to an increased proportion of lean mass relative to total body weight, thus being overall positive from a body composition perspective.<sup>11–12</sup>

Studies on metabolic surgery and CR show that, despite the muscle mass loss observed, weight reduction generally improves muscle functionality (eg, insulin sensitivity) and physical mobility.<sup>13–14</sup> Beyond the scientific study setting, where investigators tend to isolate different approaches (eg, CR, metabolic surgery or GLP-1 RA) to better understand their direct effect on clinical outcomes, it is crucial to stress that clinical guidelines for the treatment of obesity and its related complications (eg, National Institute for Health and Care Excellence in the UK) emphasise the importance of coupling enhanced physical activity with these interventions to optimise metabolic health.<sup>15–16</sup>

An example of successful combination of GLP-1 RA with physical activity for a healthy weight loss in patients with obesity was shown by Lundgren *et al*,<sup>17</sup> where lean mass loss was minimised by a combined approach. Since GLP-1 RA induce a CR state, expecting it to yield entirely different body composition outcomes than what is observed in CR studies is hard to conceive. As with CR, GLP-1 RA approaches should focus on a parallel inclusion of enhanced physical activity as an essential part of the strategy to achieving optimal health in addition to weight loss. Indeed, physical activity exerts beneficial metabolic effects beyond weight loss per se.<sup>18</sup>

## Future direction

Among the tools to counteract obesity, GLP-1 RA are an extraordinary valuable tool, but not a silver bullet, and alone, they are unlikely to solve the obesity epidemic. Combined approaches should be always taken into consideration, in real life as well as in clinical studies. Primary prevention must begin in early life, and it is worth stressing that optimal health is a result of several factors including dietary patterns (quantity, quality and timing of the meals), alongside social determinants and genetic background. Further studies combining dietary and physical activity strategies paralleled by GLP-1 RA will also help delineate how to better optimise these approaches. The long-term effects of these combined approaches should also be focusing more on their impact on body composition. Precise assessment of body

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composition is crucial for evaluating the effectiveness of weight loss interventions. Specifically, while bioelectrical impedance analysis (BIA) is a convenient tool in body composition analysis in clinical studies, dual-energy X-ray absorptiometry scan (DEXA) remains the gold standard for measuring bone mineral density, lean mass and fat mass. By using low-dose X-rays, DEXA can differentiate between these tissue types, offering a comprehensive understanding of body composition and is particularly valuable for tracking changes over time, monitoring the effects of diet, exercise or medical interventions, and to assess conditions like osteoporosis, sarcopenia and obesity. It is thus crucial to explore with more detail the body composition changes in these studies. Lastly, it is key to understand whether once achieved the weight loss target, and in absence of the medication, these patients can sustain their weight loss with lifestyle alone or as it happens with certain chronic conditions, a lifelong treatment is required.

## CONCLUSION

In conclusion, GLP-1 RA represent a promising new tool in the fight against obesity but to tackle the obesity crisis, it is crucial to use a multidisciplinary approach. Further studies will delineate how to optimise the health benefit of these treatments by combining dietary and physical activity approaches. Lifestyle changes should not be seen as alternative approaches to the problem but part of the solution with or without pharmacological help.

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