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Opinion Paper

Turning obesity into an iatrogenic disease?

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SUMMARY

This editorial argues that although GLP-1 receptor agonists have profoundly transformed obesity management, their often short-term, intermittent, or insufficiently supervised use may lead to significant loss of lean mass, weight regain after treatment discontinuation, and ultimately sarcopenia and sarcopenic obesity. It emphasizes that the weight loss achieved is not always qualitatively beneficial, since a substantial proportion may involve lean mass, while post-treatment weight regain is often predominantly fat mass. The author therefore calls for a more carefully supervised and longer-term use of these treatments, with particular attention to body composition, protein intake, muscle-strengthening physical activity, and nutritional follow-up. The central message is that GLP-1 receptor agonists should not be regarded as a miracle solution, otherwise obesity may be turned into a form of iatrogenic harm marked by weight cycling and sarcopenic obesity.

1. GLP-1-based therapies, weight regain, and body-composition concerns

GLP-1-based therapies have transformed obesity care and offer substantial benefits for appropriately selected patients. However, their rapid expansion in routine practice also raises practical questions about persistence, discontinuation, weight regain, and the interpretation of body-composition changes. The concern is not that these drugs are intrinsically harmful, but that short-term or intermittent use without a maintenance strategy may expose some patients to repeated weight fluctuations and possible nutritional or functional vulnerability.

2. Treatments designed for the long term, used in the very short term

GLP-1 agonists were initially developed for prolonged use to manage a chronic disease. But in real life, especially in non-diabetic individuals and in settings without reimbursement, the average duration of use is very short. Available data converge on several points.

In real-world conditions among non-diabetic patients, the average treatment duration is only a few months, with high discontinuation rates due to side effects or financial reasons [1]. A Danish real-world study of semaglutide presented at EASD 2025 reported that more than 50% of patients ceased treatment within one year [2]. In an American observational study in the general population, 73% of the patients had discontinued treatment at 1 year, 85% at 2 years, and 92% at 3 years! [3]. A Cleveland Clinic study published in Obesity also reported modest persistence rates, with about 20% discontinuation at 3 months and 32% within one year in real-world use of GLP-1 agonists [4]. In a German real-world study (2), 69.8% discontinued GLP-1 receptor agonist therapy (only 30.2% remained on treatment), most commonly due to little weight-loss effect (27.9%), intolerable side effects (20.9%), or financial reasons (14%), with a mean treatment duration about 3 months [1].

We are therefore faced with a strong contradiction between the theoretical framework (chronic treatment, specialized follow-up, intensive support) and what is actually happening on the ground (short, intermittent prescriptions, often driven by esthetic demand, against a backdrop of financial constraints and side effects). This deviation is not anecdotal: it directly shapes the iatrogenic risk.

3. Weight loss, but what do we really know about body composition?

In clinical trials, weight loss under GLP-1 agonists is undeniable. However, interpretation of body-composition data requires caution. Available studies show that lean mass accounts for a variable proportion of total weight loss when assessed by DEXA, notably in

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studies by Wilding et al. [5] and Hansen et al. [6]. Depending on the measurement method, lean mass loss can represent around 30–40% of total weight loss, with higher proportions when body composition is assessed by bioimpedance analysis [7]. Importantly, lean mass is not synonymous with skeletal muscle mass, and neither of these measures alone captures muscle strength or function. The current data therefore justify attention to body composition, protein intake, physical activity, and muscle function, particularly in older or frail patients, but they do not by themselves establish treatment-induced sarcopenic obesity.

Recent emerging data, including STEP-UP secondary analyses [8] and the prospective SEMALEAN study [9], suggest a more nuanced picture than simple "muscle degradation", with preserved or improved muscle-function measures reported despite reductions in lean mass. Likewise, combination strategies explored in BELIEVE [10] indicate that the quality of weight loss may be modifiable. These newer findings reinforce the need to distinguish lean-mass change from clinically meaningful muscle impairment.

4. After stopping the drug: clinically relevant weight regain

Weight regain after treatment discontinuation is well documented and reflects, at least in part, the chronic relapsing nature of obesity.

Weight regain after discontinuation is well documented. In STEP 1, patients who had lost an average of 17.3% (± 9.3%) of their body weight regained about 11.6% (± 6.1%) at 120 weeks after discontinuation [11]. In SURMOUNT-4, withdrawing tirzepatide led to substantial regain of lost weight (+14.0%; 95% CI, 12.8 to 15.2), whereas continued treatment maintained and augmented initial weight reduction [12]. A recent narrative review suggested that about 70% of lost weight may be regained within one year in the available randomized withdrawal literature [13]. More recently, a 2026 BMJ systematic review and meta-analysis [14] estimated mean weight regain after cessation at about +0.4 kg/month overall, and up to +0.8 kg/month after semaglutide or tirzepatide; follow-up for newer incretin mimetics rarely exceeded 12 months, so longer-term trajectories remain uncertain. These data strongly support the need to view obesity as a chronic disease and to plan maintenance strategies when treatment is interrupted.

It is important, however, to specify what "structured care" meant in these trials. In the randomized withdrawal studies that most directly inform the rebound question, weight regain occurred despite continued standardized lifestyle support: in STEP 4 [15] and SURMOUNT-4 [12], participants in both groups continued to receive dietary counseling, a target energy deficit of about 500 kcal/day, and encouragement to perform at least 150 min/week of physical activity, yet those switched to placebo regained weight. By contrast, the STEP 1 extension is less informative on this point because withdrawal of semaglutide was accompanied by discontinuation of the initial structured lifestyle intervention [11]. Equally important, these programs were not equivalent to a full multidisciplinary obesity pathway with systematic screening and treatment of eating disorders or specialized psychological care; major psychiatric disorders were generally excluded, and dedicated eating-disorder-focused interventions were not part of the trial design.

Another important point is that participants enrolled in the pivotal obesity trials of GLP-1-based therapies had marked obesity at baseline rather than mild excess weight, with mean BMI values generally in the 38–40 kg/m^2 range (e.g. 37.9 kg/m^2 in STEP 1 (11), 38.4 kg/m^2 in STEP 4 (15), 40.1 kg/m^2 in STEP 10 [16], and 38.3 kg/m^2 in SCALE Obesity and Prediabetes [17]). A similar baseline severity was observed in the SURMOUNT programme, with mean BMI values of about 38.0 kg/m^2 in SURMOUNT-1 and 38.4 kg/m^2 in SURMOUNT-4 [12,18].

The weight-maintenance literature, for its part, clearly indicates that ongoing visits and follow-up are major determinants of long-term weight stability [19]. The pre-GLP-1 weight-cycling literature also suggests that repeated cycles of weight loss and regain may unfavorably affect body composition over time, with a relative increase in fat mass and a relative decrease in lean mass in some settings, as modeled notably by Hall KD et al. [20] and Dulloo AG et al. [21]. However, extrapolating these data directly to GLP-1 discontinuation requires caution. We currently lack robust post-cessation studies assessing skeletal muscle mass, muscle function, or the risk of sarcopenic obesity after weight regain. The concern should therefore be framed as a plausible clinical risk that warrants monitoring, particularly in older, frail, or nutritionally vulnerable patients, rather than as an established categorical outcome.

5. Could repeated discontinuation increase body-composition risk in vulnerable patients?

This issue is therefore clinically relevant, not because sarcopenic obesity after discontinuation has been demonstrated, but because several vulnerable domains may converge in some patients: reduction in lean mass during active weight loss, subsequent weight regain after stopping therapy, low physical activity, inadequate protein intake, and pre-existing frailty or comorbidity. These scenarios justify closer monitoring of nutritional status, body composition when available, and muscle function in patients at higher risk.

Intermittent prescribing of GLP-1 agonists, without any long-term maintenance strategy, should therefore be regarded as a situation in which weight regain is likely and body-composition deterioration is plausible, particularly in patients already at risk (older adults, frail or malnourished patients, and sedentary individuals).

6. Nutritional vulnerability in people with obesity: an often overlooked issue

To date, neither clinical trials nor real-world studies have clearly demonstrated a specific syndrome of malnutrition caused by GLP-1 receptor agonists. Nonetheless, in people living with obesity, nutritional vulnerability should be considered when reduced intake, gastrointestinal side effects, rapid weight loss, low protein intake, or pre-existing frailty coexist. In such settings, the relevant concern is not low BMI alone, but the possibility of inadequate nutrient intake, loss of strength or function, and unrecognized micronutrient deficiencies. This justifies clinical vigilance, dietary assessment, and targeted supplementation when indicated.

Unsupervised use of GLP-1 agonists, especially when combined with highly restrictive diets, may therefore create an unfavorable situation: rapid weight loss, insufficient protein or micronutrient intake, suboptimal muscle preservation, and later weight regain.

A shared responsibility: moving beyond the "miracle injection" mindset.

Given these findings, the question is not to demonize GLP-1 agonists. These drugs have clear, legitimate indications in type 2 diabetes and obesity and have demonstrated important benefits when prescribed within specialized, multidisciplinary, and long-term management. At the same time, their benefits do not remove the need to anticipate discontinuation, maintenance, and nutritional monitoring in routine care. There is therefore an urgent need to:

Recent trials such as STEP-UP [8] and REDEFINE-1 [22] also highlight the rapid therapeutic progress of this field and remind us that any discussion of limitations should be balanced against the substantial efficacy of these newer agents and combinations.

1. **Recognize discontinuation as a critical phase of care**
   - Short or intermittent use of GLP-1 agonists should prompt anticipation of weight regain and closer follow-up, rather than being treated as a benign interruption.
2. **Tighten indications and prescribing conditions**
   - Limit these medications to structured obesity care with specialist follow-up.
   - Exercise heightened caution in older adults, frail patients, and those with low caloric or protein intake or pre-existing nutritional vulnerability.
3. **Put muscle function and nutritional quality at the center of the strategy**
   - Measure and monitor body composition whenever possible, while recognizing its limitations.
   - Systematically promote resistance/strength training, adequate protein intake, and functional assessment when clinically relevant.
   - Treat preservation of muscle function and nutritional quality as therapeutic goals, alongside weight loss itself.

The data clearly show that ongoing visits and nutritional follow-up are key to long-term weight stabilization. However, evidence on which post-cessation strategies best prevent rebound after stopping weight-management medications remains limited. Stopping a GLP-1 agonist without behavioral support or a maintenance plan is therefore a foreseeable cause of weight regain.

7. A call for balanced and long-term obesity care

Obesity pharmacotherapy should not repeat the mistakes of the past, but neither should current concerns be overstated. The central issue is not that GLP-1-based therapies have been shown to cause sarcopenic obesity, but that obesity is a chronic disease and that repeated cycles of treatment interruption and weight regain may create avoidable clinical problems if long-term strategies are absent. Weight cycling itself has been associated with adverse cardiometabolic correlates in prior literature [23]. The message for clinicians is therefore a balanced one: GLP-1 agonists are highly effective therapies with major benefits in appropriately selected patients, but discontinuation, nutritional follow-up, physical activity, and muscle-function monitoring deserve far more attention than they currently receive in routine care.

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Conflict of interest

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