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TOPICAL REVIEW

Adaptations of glucagon-like peptide-1 receptor agonist-induced weight loss, drivers of weight regain and future directions of therapeutics

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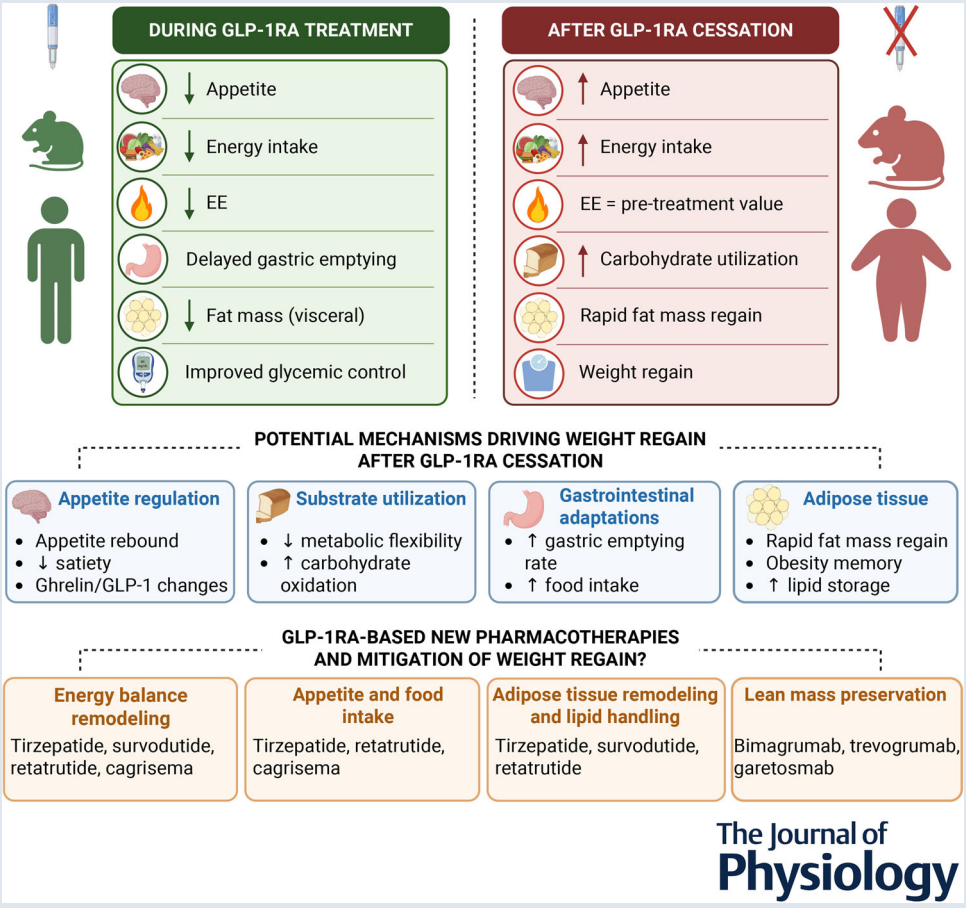

Abstract figure legend During GLP-1RA treatment reduced appetite and energy intake, delayed gastric emptying, decreased visceral fat mass and improved glycaemic control contribute to weight loss. After treatment cessation these benefits are partially or completely reversed, resulting in weight regain, accompanied by increased appetite and energy intake, altered substrate utilization and rapid fat mass regain. Potential mechanisms underlying weight regain include appetite dysregulation, reduced metabolic flexibility, gastrointestinal adaptations and adipose tissue remodelling (obesity memory and enhanced lipid storage). Emerging GLP-1RA-based combination therapies may provide greater and more durable weight loss by targeting energy balance, appetite regulation, adipose tissue remodelling and lean mass pre-

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servation. Whether these therapies can mitigate weight regain after treatment discontinuation remains to be determined. Abbreviations: EE: energy expenditure, GLP-1RA: glucagon-like peptide-1 receptor agonist.

Abstract Obesity, characterized by excess gain in body fat, alters energy balance and metabolic health. Weight loss is an effective strategy to favourably restore metabolic parameters in obese condition, and this can be achieved through caloric restriction, exercise, bariatric surgery and pharmacotherapy. Recently, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and associated combination therapies have proven to be effective weight loss inducers that also contribute to improvements in glycaemia and lipidaemia. However, side effects and socioeconomic barriers often lead to treatment discontinuation, which raises concerns about the effects of cessation on metabolic health. Regardless of the weight loss method, weight regain is common, although its underlying mechanisms remain unclear. Recent research has explored factors such as metabolic adaptation, shifts in appetite-related hormones and changes in the adipose tissue to better understand these consequences. This review summarizes current knowledge on the metabolic and physiological responses to GLP-1RA-induced weight loss and provides insight into potential mechanisms of weight regain after GLP-1RA withdrawal. It also explores how emerging GLP-1RA-based combination therapies might help mitigate this challenge.

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Introduction

Obesity. Obesity is defined by the World Health Organization (WHO, 2026) as an abnormal or excessive accumulation of fat that presents a significant health risk. According to the World Obesity Federation(2024), nearly 3 billion people were considered overweight, including almost 1 billion with obesity (880 million adults and 159 million children and adolescents aged 5–19 years). Overweight and obesity are major health risk factors and are associated with various complications, including cardiovascular disease, type 2 diabetes mellitus (T2DM), hypertension and cancers (Salam et al., 2023). Due to the increasing prevalence and the risks associated, various strategies have been developed to promote weight loss.

Treatment of obesity. Several therapeutic strategies are available to manage obesity, including lifestyle modifications, bariatric surgery and pharmacological treatments. Lifestyle interventions, such as caloric restriction and intermittent fasting, can achieve meaningful weight loss ($\geq$5%) and improve metabolic outcome (Dwaib et al., 2021). However, long-term maintenance of weight loss remains challenging. In a retrospective observational study 57% of adults with obesity discontinued their dietary behavioural weight loss treatment within 6 months (Colombo et al., 2014). Bariatric surgery, particularly Roux-en-Y gastric bypass and sleeve gastrectomy, is currently the most effective intervention for inducing sustained weight loss and remission of obesity-related comorbidities

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(King et al., 2018; Noria et al., 2023). However, these surgeries are deemed invasive, and eligibility criteria limit only those with a body mass index (BMI) >40 (with no comorbidities) or ≥35 (with metabolic disease comorbidities), excluding a large portion of patients who are forced to rely on other methods for weight loss (Obesity Canada, Practice Guidelines).

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as a promising pharmacological approach to treat obesity that can achieve meaningful weight loss with similar effects to bariatric surgeries (Sabatella et al., 2025). Endogenous GLP-1 is an incretin hormone secreted by the upper small intestinal L-cells in response to nutrient ingestion where it enhances glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying and reduces appetite through central nervous system pathways (Zheng et al., 2024). GLP-1RAs, such as semaglutide, exenatide and liraglutide, are synthetic analogues with prolonged activity (semaglutide with a 160-h half-life in humans) that harness these endogenous physiological effects. Clinical trials have demonstrated that once-weekly semaglutide leads to significant weight loss in individuals with obesity and T2DM, along with improvements in glycaemic control, lipid metabolism and blood pressure (Rubino et al., 2021; Wilding et al., 2022). These benefits make GLP-1RAs a central component of modern anti-obesity pharmacotherapy. Building on the efficacy of GLP-1RAs, newer therapies have emerged with greater weight loss and glycaemic control potential. These therapies target multiple hormonal pathways, including agonism of glucose-dependent insulinotropic peptide (GIP), glucagon and amylin, and inhibition of activin type II receptors. For example, the dual receptor agonist GLP-1/GIP resulted in a 6.5% increase in relative body weight loss compared with semaglutide in adults with obesity without T2DM (Aronne et al., 2025) and increased energy expenditure (EE) and fat oxidation compared to semaglutide in diet-induced obese mice (Coskun et al., 2018). Similarly, 40 weeks of treatment with the triple receptor agonists GLP-1/GIP/glucagon retatrutide in adults with overweight and obesity and with T2DM resulted in 15.3% weight loss and was accompanied by improvements in glycaemic control, blood pressure and lipid profiles (Bajaj et al., 2026).

Trajectory of therapy. Although incretin hormone-based therapies have proven to be an efficient weight loss solution, their continued usage is often an issue. Up to 81% of patients with overweight and obesity discontinued GLP-1RAs (liraglutide, semaglutide and tirzepatide)–based treatments after 1 year (Rodriguez et al., 2025). A similar observation was made in another study, where discontinuation rate was 45.2% and 64.7%, after 12 and 24 months, respectively (Weiss et al., 2022). This discontinuation can be explained by different factors. First, GLP-1RAs are responsible for a variety of side effects, the most common being gastrointestinal disorders (nausea, diarrhea, vomiting, constipation, abdominal pain and dyspepsia) (Filippatos et al., 2014; Sun et al., 2015). In a proprietary, multinational real-world evidence (RWE) survey, gastrointestinal-related problems were the leading two reasons reported by 194 patients for stopping GLP-1RAs (Sikirica et al., 2017). Other adverse side effects include injection site reaction (rash, erythema), chronic pancreatic damage, upper respiratory tract infection, urinary tract infection and headache (Filippatos et al., 2014). Socioeconomic reasons also play a role, as they may limit prolonged access to adequate healthcare coverage (Do et al., 2024).

What happens after the cessation of treatment? High rates of GLP-1RA treatment cessation raise critical questions regarding metabolic consequences, an area only recently receiving attention. A pioneering study addressing this demonstrated that after 68 weeks of subcutaneous injections of weekly semaglutide in 1961 adults with obesity and without T2DM, 52 weeks of discontinuation resulted in weight regain, with patients regaining two-thirds of their prior weight loss as well as return to pretreatment levels for blood pressure and HbA1c. Interestingly, levels of C reactive protein, cholesterol, LDL, HDL and VLDL increased but remained below prior treatment values (Wilding et al., 2022). The reason behind weight regain after GLP-1RAs is unclear. It is important to note that weight regain is also observed with other interventions such as caloric restriction and bariatric surgery (Marlatt et al., 2017; Noria et al., 2023). Therefore this review has been inspired by observations during weight loss and regain after these interventions. Additionally with the development of combination therapies, there is a growing need to contextualize these approaches alongside GLP-1RA monotherapy. Although these agents may improve weight loss outcomes, the underlying mechanisms and their impact on weight regain after cessation remain unclear. Understanding how these emerging medications work is critical because it may influence long-term success of weight maintenance and guide the future of pharmacotherapies targeting obesity and T2DM.

This narrative review aims to characterize the metabolic and physiological responses to weight loss after GLP-1RA therapy and identify potential mechanisms of weight regain with the cessation of therapy, and to assess the potential of emerging GLP-1RA-based therapies on weight maintenance. We review the metabolic adaptationoccurring during and after GLP-1RA treatment with a focus on EE, appetite change and loss of lean and fat mass in preclinical and clinical models.

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Here we discuss peer-reviewed original studies and clinical trials examining physiological, metabolic and behavioural responses during GLP-1RA treatment and withdrawal, as well as newer combination therapies. The studies were selected based on their relevance, with priority given to recent publications. Relevant reviews were also screened to identify additional studies. Due to the differences in lifespan and metabolism between rodents and humans, preclinical and clinical studies are discussed separately throughout the review. The review structure was designed to present animal and human studies independently within each section, thereby avoiding a direct comparison between both models.

Physiological effects of GLP-1RAs treatment and cessation

Metabolic adaptation. Both weight loss and gain initiate physiological responses, often referred to as metabolic adaptations, which include alterations in EE, substrate utilization and hormonal signalling that affects appetite (Hall et al., 2007; Martins et al., 2023). Here we present recent findings on the effects of GLP-1RAs on EE, fat and carbohydrate oxidation and appetite regulation in pre-clinical and clinical models.

Energy expenditure. A first important aspect of metabolic adaptation is the subsequent shift in EE during a period of weight change. EE consists of four categories of measurements: resting metabolic rate or resting EE, thermic effect of feeding and exercise and adaptative thermogenesis (Poehlman & Horton, 1989; National Academies of Sciences et al., 2023).

Weight loss is consistently accompanied by a reduction in total daily, resting and non-resting EE, regardless of whether it is achieved through caloric restriction (Falkenhain et al., 2025), exercise (Martins, et al. 2022a) or bariatric surgery (Falkenhain et al., 2025). Energy intake is a key component of energy balance (delta energy = energy intake – EE); however EE is equally critical in predisposing individuals to weight regain because sustained reductions in EE can contribute to a positive energy imbalance and facilitate weight regain (Blomain et al., 2013), especially if caloric intake is not proportionally reduced.

Preclinical studies. As body mass declines so does EE. Semaglutide administration (dose escalated to 9.7 nmol/kg for 11 days) to male C57BL/6J mice after 20 weeks on a high-fat diet (HFD; 45% of calories from fat) showed a reduction in EE until day 6 of treatment, whereas the weight-matched group (pair fed to match the semaglutide food intake) had lower EE throughout the entire treatment period (Gabery et al., 2020). These findings indicate that semaglutide-induced weight loss reduces EE temporarily and attenuates the continuously lower EE observed in the weight-reduced match group. Considering food intake is the same between both groups, the authors from that study suggested that these divergences between both groups may reflect differences in gut nutrient absorption and increased faecal energy loss in the semaglutide-treated mice.

Conversely, after 4 weeks of semaglutide treatment (titrated to 10 nmol/kg from day 3) in obese male C57BL/6J mice (12 weeks fed a 45% HFD), EE reduced in both the semaglutide-treated and pair-feeding groups compared to the vehicle group, suggesting a loss in weight results in less metabolically active tissue (Jeromson et al., 2025). Interestingly, EE was comparable between groups 5 weeks after treatment cessation. However, this prolonged washout period may have missed acute changes in EE that could help explain mechanisms of weight regain, in which increased food intake after GLP-1RA discontinuation, combined with lower EE, would promote weight gain.

The underlying mechanisms and physiological consequences of GLP-1RA effects on EE remain unclear. GLP-1 is well known to act on brain regions involved in the control of feeding and may also influence overlapping neural circuits that regulate EE. A reduction in EE with semaglutide treatment (15 and 30 μg/kg on days 1 and 2, followed by 60 μg/kg until day 10) has been attributed to GLP-1 action on Adcyap1^{+} neurons within the area postrema (AP) and nucleus of the solitary tract (NTS) (Teixidor-Deulofeu et al., 2025). Deletion of GLP-1R in Adcyap1^{+} neurons of the AP or NTS in lean mice impaired semaglutide-induced weight loss and reductions in food intake, resulting in no change in EE. These findings support the concept that reduced food intake plays a primary role in the weight loss observed with GLP-1RA treatment.

Collectively, preclinical studies suggest that GLP-1RAs induce a reduction in EE, possibly via weight loss and changes in food intake more than the direct effect of GLP-1RAs. If this decrease in EE is sustained after treatment discontinuation, this could easily lead to a positive energy balance and contribute to weight regain. However, additional studies are required to draw definitive conclusions. Future work could assess that cessation period in depth or administer other formulations of GLP-1RA or dosing regimens that may not induce effects on EE in lean or obese insulin-resistant mice. To expand on this, new GLP-1RA-based medicines are discussed later in this review. Data from these studies are summarized in Table 1.

Clinical studies. Acute (3 days) liraglutide (0.6 mg/day) administration showed no differences in 24-h EE in patients aged ∼60 years with T2DM and obesity compared to placebo (Harder et al., 2004). To note the patients who received this treatment of liraglutide reported no

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Table 1. Summary of preclinical metabolic adaptations during GLP-1RA treatment

Author	Population	Treatment	Weight loss	Glycaemic control	Effect on EE	Effect on substrate use	Effect on appetite	Notes
Gabery et al. (2020)	Obese male C57BL/6J mice	Semaglutide 9.7 nmol/kg for 11 days	17%–18% weight loss	N/A	↘ EE until day 6	↘ RER (increased fat oxidation)	↘ Food intake	
Jeromson et al. (2025)	Obese male C57BL/6J mice	Semaglutide increased to 10 nmol/kg for 4 weeks and withdrawal of treatment for 6 weeks	19% weight loss which was regained within 3 weeks of withdrawal	Improved glucose tolerance that did not persist after withdrawal	↘ EE during treatment and no difference with control group after withdrawal	No change in RER during treatment but increased RER after 5 weeks of withdrawal	↘ Food intake during treatment period	
Teixidor-Deulofeu et al. (2025)	Lean male mice without or with a deletion of Adcyap1$^+$ neurons within the AP and NTS	One acute semaglutide injection 60 µg/kg	10% weight loss No weight loss was observed when Adcyap1$^+$ is knocked out	↘ Blood glucose with or without Adcyap1$^+$ knockout	↘ EE attributed to AP and NTS Adcyap1$^+$ neurons	↘ RER attributed to AP and NTS Adcyap1$^+$ neurons	↘ Food intake attributed to AP and NTS Adcyap1$^+$ neurons	
Zhao et al. (2019)	Obese male Wistar (control) and Goto-Kakizaki	Liraglutide low (107 nmol/kg/day) or high (320 nmol/kg/day) dose	No major change in body weight	↘ Fasting and postprandial blood glucose	N/A	↗ Fatty acid β-oxidation for the high dose	↘ Food intake during the first week of treatment	
Sisley et at. (2014)	Obese male mice with neuronal or visceral nerve-specific depletion of GLP-1R in the CNS	Liraglutide 400 µg/kg/day for 14 days	About 5 g of weight loss but no weight loss with CNS GLP-1R depletion	Improved glucose tolerance with and without CNS GLP-1R depletion	N/A	N/A	↘ Food intake attributed to CNS GLP-1R	

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Table 1. (Continued)

Author	Population	Treatment	Weight loss	Glycaemic control	Effect on EE	Effect on substrate use	Effect on appetite	Notes
Adams et al. (2018)	Male and female lean and obese mice with deletion of GLP-1R in glutamatergic neurons or GABAergic neurons	Liraglutide 400 µg/kg/day for 24 h or 14 days	6% acute and 10% chronic weight loss attributed to GLP-1R in glutamatergic neurons	N/A	N/A	N/A	↘ Food intake acutely and chronically attributed to GLP-1R in glutamatergic neurons	
Kooij et al. (2023)	Lean male pitx3-cre$^{+/-}$ mice (C57BL/6J background)	Semaglutide 1 mg/kg once	N/A	N/A	N/A	N/A	↘ Chow intake increases VTA dopamine activity during reward collection	↗ VTA dopamine activity during reward collection

CNS, central nervous system; EE, energy expenditure; GLP-1RA, glucagon-like peptide-1 receptor agonist; RER, respiratory exchange ratio; VTA, ventral tegmental area.

changes in weight after 8 weeks of treatment. Therefore, a liraglutide dose of 0.6 mg/day may be insufficient to elicit measurable changes in EE; however, it supports the notion that weight loss is necessary to reduce EE, implying that this decline is driven by weight loss rather than by the direct effects of GLP-1RAs on EE pathways. Moreover, the lack of long-term measurements after the 8 weeks of treatment makes it difficult to definitively conclude on the effect of GLP-1RAs on EE.

In a two 5-week crossover study in men and women aged 18–75 years with obesity, chronic treatment with liraglutide (1.8 or 3 mg/day) resulted in lower 24-h EE and sleeping metabolic rate compared to the placebo group when measurements were taken 1 or 2 days (van Can et al., 2014). A 4- and 12-week treatment with liraglutide (1.8 mg/day) lowered EE in male and female patients with overweight and obesity as well as T2DM, aged 18–69 years (Eyk et al., 2020). This decrease in EE is not sustained after 26 weeks oftreatment. Interestingly, when normalized to lean mass loss, EE was lower in liraglutide treated group only at the 4-week timepoint. This suggests that EE initially decreases independently of lean mass loss but over time becomes driven by it. Six-month treatment of liraglutide (3.0 mg/day) in adults with non-diabetic obesity produced no changes in EE (Basolo et al., 2025). Collectively, this suggests that EE is affected by treatment initially (until week 12) but normalizes overtime, where no difference was observed after 26 weeks of treatment. Importantly, food intake is a critical component to consider and may help to determine observed differences. It is well known that GLP-1RAs act as appetite suppressants, but it is possible that the appetite is restored after chronic treatment; however this remains to be tested.

Investigating a long-acting GLP-1RA such as semaglutide offers advantages due to the peptide's longer half-life. In a crossover design study with 12 weeks of semaglutide once weekly (0.25 mg the first 4 weeks, then 0.5 mg the next 4 weeks and finally 1 mg the last 4 weeks), 30 men and women with obesity (BMI from 30 to 45 kg/m^2) demonstrated lower resting metabolic rate 3 days after treatment (Blundell et al., 2017). But once it normalized to lean mass, the difference in resting metabolic rate was no longer detectable, supporting the idea that lean mass loss may be responsible in manipulating EE measurements. Moreover, this leads to the idea that lower EE and greater lean mass loss may drive greater weight rebound.

Together, these studies span timepoints ranging from 3 days to 26 weeks of treatment, allowing for a broader understanding of treatment effects on EE. However, the effects of GLP-1RAs on EE remain inconclusive. In general acute treatment does not appear to alter EE, whereas chronic GLP-1RA exposure is associated with reduced EE in conjunction with weight loss. Once weight loss

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stabilizes changes in EE may no longer be observed. The duration of GLP-1RA treatment might be a key determinant of EE adaptation. This raises the possibility that early treatment cessation could increase susceptibility to weight regain. To note, the studies discussed have not reported the effects on food intake or lean mass that could drastically affect EE. The thermic effect of feeding contributes to ∼10% of total EE, which may be an important aspect that is greatly overlooked in these clinical trials. Moreover, overfeeding and underfeeding studies demonstrate an increase or decrease in resting metabolic rate (Poehlman & Horton, 1989). Therefore, larger studies with more attention to dose, timing, weight loss and food intake in individuals with and without obesity and T2DM are needed to further determine the effects of GLP-1RA therapies on EE. Data from these studies are summarized in Table 2.

Substrate utilization/respiratory exchange ratio. Although absolute EE is important, it is equally critical to consider the nutrient sources contributing to its measurements. The respiratory exchange ratio (RER) is a metric that gives more information on where energy usage is derived. RER is based on oxygen consumption and carbon dioxide production to determine the relative contribution of carbohydrate and lipid oxidation to EE. RER values equal to 1 represent the oxidation of glucose molecules, where the production of carbon dioxide is equal to the consumtpion of dioxygen molecules. In contrast, the oxidation of a fatty acid uses 23 dioxide molecules but produces only 17 carbon dioxide molecules, resulting in the ratio of 0.7. Therefore, a ratio closer to 1 or 0.7 indicates the primary use of carbohydrates or lipids, respectively, as a source of energy (Nelson et al., 2015).

Preclinical studies. *In vivo* studies in diet-induced obese male C57BL6/J mice reported that both semaglutide (once daily titrated to 9.7 nmol/kg for 2 weeks) and pair feeding lowered RER, indicating increased fat oxidation (Gabery et al., 2020). However, the time when this effect was observed differed between both groups. During the dark-phase cycle semaglutide-treated mice exhibited a more pronounced reduction in RER, whereas during the light-phase cycle, pair-fed mice had lower RER values than semaglutide-treated animals. This latter observation was attributed to the prolonged fasting in the pair-fed group, as these mice consumed all their food early in the dark phase. This highlights the strong influence of feeding behaviour and timing on RER measurements. In contrast, at similar doses of semaglutide (10 nmol/kg for 1 month), RER did not change in diet-induced obese male mice compared to pair-fed or control mice (Jeromson et al., 2025). Similar to the point raised for EE measurements, different timing protocols during experimental design could be responsible for the observed effects. RER may change with food intake and during acute treatment, and return to baseline levels after long-term exposure. Interestingly, when RER is assessed 5 weeks after discontinuation of semaglutide treatment in diet-induced obese male mice, both previously treated semaglutide and pair-fed mice exhibited an increase in RER during the dark phase, suggesting that weight regain, independent of treatment, promotes glucose utilization (Jeromson et al., 2025).

Interpretation of these findings is challenged by the limitations of relying on RER for absolute rates of carbohydrate or fat oxidation, because it only reflects the predominant source of fuel being oxidized at a given time. Additionally, RER assumes no contribution of protein oxidation (Gan et al., 2025), but during times of rest or caloric restriction, contribution of protein oxidation increases (Wang et al., 2026). Finally, RER values are highly sensitive and can shift depending upon the timing of meals as well as the metabolic status of animals (i.e. hyperglycaemia, hyperlipidaemia). These limitations highlight the need for direct measurements of substrate utilization to more accurately assess the metabolic effect of GLP-1RAs. Male Wistar (control) and Goto-Kakizaki (GK; non-obese, non-hyperglycaemic model of diabetes) rats were fed a HFD for 8 weeks and then treated with either low (107 nmol/kg/day) or high (320 nmol/kg/day) doses of liraglutide for 12 weeks. High-dose liraglutide treatment increased fatty acid oxidation in skeletal muscle, as assessed by the direct measurement of β-oxidation using a $3H_2O$ radiolabelled tracer, compared with vehicle-treated GK rats (Zhao et al., 2019). As GLP-1Rs are not located in the skeletal muscle (Hammoud & Drucker, 2023), mechanisms of direct action of GLP-1RAs on increasing fatty acid oxidation are unknown. Although, this could be driven by other metabolically active tissues like the liver and kidney. Moreover it does not appear that GLP-1RA-induced changes in RER may drive mechanisms of weight regain and nutrient utilization adaptations, at least in rodents. However, it is possible that fat oxidation increase will not be sustained after treatment cessation, which might affect energy storage and promote fat accumulation. RER and substrate oxidation need to be considered to definitively determine if mechanisms of weight regain are driven by RER.

Overall, preclinical data examining the effects of GLP-1RAs on substrate utilization remain limited and heterogeneous. Differences in feeding behaviour, timing of measurements, disease state and methodological approaches likely contribute to divergent findings. Future work combining precise measurements of substrate utilization and food intake, both during treatment and after withdrawal, will be essential to determine whether GLP-1RAs exert direct effects on fuel selection or whether

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Table 2. Summary of preclinical metabolic adaptations during GLP-1RA treatment

Author	Population	Treatment	Weight loss	Glycaemic control	Effect on EE	Effect on substrate use	Effect on appetite	Notes
Harder et al. (2004)	Men and women aged ∼60 years with type 2 diabetes and obesity	Liraglutide 0.6 mg/day for 3 days	No changes in weight	N/A	No differences in 24-h EE	N/A	N/A	
Van Can et al. (2014)	Men and women aged 18–75 years with obesity	Liraglutide 1.8 or 3 mg/day for 5 weeks	2.1 and 2.5 kg of weight loss for 1.8 and 3 mg/day, respectively	↘ Fasting and postprandial blood glucose and glucagon	↘ EE and RMR	↘ RER with 1.8 mg/day ↘ Carbohydrate and protein oxidation for both doses ↗ Fat oxidation with 1.8 mg/day	16% ↘ in energy intake ↘ Hunger ↗ Fullness and satiety	
Eyk et al. (2020)	Men and women aged 18–69 years with overweight or obesity and type 2 diabetes	Liraglutide 1.8 mg/day for 26 weeks	4.3 kg after 26 weeks (2.1 kg of lean mass)	No difference in fasting blood glucose	↘ EE at 4 and 12 weeks of treatment No differences after 26 weeks	No differences in RER and glucose and lipid oxidation, which could be attributed to type 2 diabetes	N/A	Normalized to lean mass; EE is decreased only at week 4
Basolo et al. (2025)	Men and women ∼49 years with non-diabetic obesity	Liraglutide 3.0 mg/day for 6 months	10% body weight loss	N/A	No differences in EE	↘ Carbohydrate oxidation ↗ Fat oxidation Protein oxidation is unchanged	N/A	
Blundell et al. (2017)	Men and women >18 years with obesity	Semaglutide (increased to 1 mg) once weekly for 12 weeks	5 kg of weight loss (1.1 kg of lean mass)	N/A	↘ RMR	N/A	24% ↘ *ad libitum* energy intake ↘ Subjective appetite	Normalized to lean mass; RMR is not decreased

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Table 2. (Continued)

Author	Population	Treatment	Weight loss	Glycaemic control	Effect on EE	Effect on substrate use	Effect on appetite	Notes
Horowitz et al. (2012)	Men and women aged 18–65 years with type 2 diabetes	Liraglutide treatment once daily titrated to 1.8 mg for 4 weeks	1.3 kg of weight loss	No differences in fasting blood glucose	No differences in 24-h REE	N/A	↘ Pre-meal hunger ↘ PYY No changes in ghrelin and GIP	
Kadouh et al. (2019)	Men and women aged 18–65 years with non-diabetic obesity	Liraglutide once daily titrated to 3.0 mg for 16 weeks	5.8 kg of weight loss (1.3 kg of lean mass)	N/A	N/A	N/A	↗ Postprandial PYY levels while simultaneously ↘ Prospective food consumption, desire to eat and maximum-tolerated gastric volume	
Iepsen et al. (2015)	Men and women aged ∼46 years with healthy obesity that underwent a diet-induced 12% weight loss	Liraglutide once daily titrated to 1.2 mg/day for 52 weeks	Additional 2.3 kg weight loss	↘ Fasting glucose	N/A	N/A	↘ Decline in GLP-1 levels and leptin ↗ Postprandial PYY	

EE, energy expenditure; GIP, glucose-dependent insulinotropic peptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; RER, respiratory exchange ratio; RMR, resting metabolic rate.

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observed changes reflect adaptation to weight loss. Data from these studies are summarized in Table 1.

Clinical studies. Clinical studies investigating the effects of GLP-1RAs on substrate utilization have primarily relied on measurements of RER and indirect calorimetry-derived oxidation rates thatproduce heterogeneous results. In men and women with obesity, daily administration of liraglutide (1.8 mg/day for 5 weeks) reduced RER, and no effect was detected in those treated with 3.0 mg/day for the same time frame (van Can et al., 2014). However, both liraglutide doses were associated with reductions in carbohydrate and protein oxidation, but higher fat oxidation was observed only in the 1.8 mg/day group compared to placebo treatment. As both doses induced a similar reduction in energy intake (∼16%) relative to placebo, these findings raise the possibility that liraglutide dose may influence substrate utilization beyond its effect on nutrient intake alone.

Conversely, RER was not different when evaluated at 0, 4, 12 and 26 weeks throughout liraglutide treatment (1.8 mg/day) in men and women with T2DM and overweight and obesity (Eyk et al., 2020). Particularly, individuals with T2DM characteristically have lower baseline RER values compared to normoglycaemic individuals, which may limit the ability to detect any shift in substrate usage. Thus, this could explain why changes in RER were observed in individuals with obesity but not in those with T2DM comorbidity. Data from Basolo et al. support this as carbohydrate oxidation was reduced accompanied by increased fat oxidation, whereas protein oxidation remained unchanged after 6 months of liraglutide treatment (3.0 mg/day) in 11 patients with non-diabetic obesity (Basolo et al., 2025). These changes occurred with a 10% body weight loss but in absence of alteration in EE, suggesting that liraglutide administration may influence fuel selection independently of the total energy output during longer treatment periods.

Similar to preclinical work, clinical studies assessing substrate oxidation during GLP-1RA treatment report inconsistent effects on RER values. However, when considered collectively the data suggest a trend towards increased fat oxidation, with outcomes influenced by dose, treatment duration and glycaemic status. If this increase in fat oxidation during weight loss is not sustained after treatment cessation, this might promote fat storage and ultimately contribute to fat mass regain. To note, the mechanism underlying these changes in RER remains unclear, and it is difficult to separate direct GLP-1RA effect from adaptations to reduced energy intake and weight loss. As observed in preclinical studies, longitudinal assessments of substrate oxidation after treatment discontinuation may provide critical insight into whether these changes persist. Moreover, additional clinical studies comparing RER in patients with obesity and T2DM treated with semaglutide *versus* liraglutide may help determine whether different GLP-1RA formulations demonstrate consistent effects, as very few studies have investigated their effects on RER. Data from these studies are summarized in Table 2.

Appetite and hormonal regulation. A consistent limitation of the studies discussed is the lack of consideration for how changes in food intake affect energy homeostasis. Appetite, as a metabolic adaptation, corresponds with weight changes. For example canagliflozin, a sodium-glucose cotransporter 2 inhibitor, used alongside diet and exercise in 152 human participants with T2DM for an average of 4 years (BMI: ∼31 kg/m^2) demonstrated increased appetite by ∼100 kcal/day/kg of lost weight (Polidori et al., 2016). Many regulators modulate food intake changes and thereby appetite-regulating hormones, including those involved in satiety (leptin, Peptide YY, GLP-1), hunger (ghrelin) and glucose and metabolic regulation (insulin, glucagon, GLP-1, amylin). Preclinical and clinical studies have evaluated the effects of different weight loss interventions on these hormones. Lin et al. reported decreases in fasting and post-glucose load levels of glucagon, amylin, PYY and GLP-1 with weight loss, whereas ghrelin increased at 3 months and persisted through 6 months in 253 individuals with overweight/obesity and prediabetes that were randomized to one of three 25% isocaloric-restricted (Lin et al., 2024). Particularly, greater reductions in amylin and GLP-1, or increases in ghrelin levels, were associated with weight regain. Other reviews are dedicated to changes in appetite-regulating hormones in weight loss and gain (Busetto et al., 2021; Skoracka et al., 2025; Jin et al., 2025), but a few have specifically attributed these changes to GLP-1RA therapies.

Preclinical studies. Mechanistic investigations show GLP-1RA treatment reduces food intake and suppresses appetite in rodents through central pathways (Gabery et al., 2020). Central neuronal or visceral nerve depletion of GLP-1Rs in male mice fed a high-fat and high-sucrose diet eliminated the anorectic and weight loss effects of liraglutide (dose increased to 1000 μg/kg for 14 days) independent of its glucose lowering effects (Sisley et al., 2014). Acute (24 h) and chronic (2 weeks) liraglutide administration (400 μg/kg) in lean and obese mice of both sexes revealed that reductions in food intake are mediated by GLP-1Rs in glutamatergic neurons (Adams et al., 2018). Besides appetite, GLP-1RAs affect the brain's food reward system. Acute semaglutide administration (1 mg/kg) in lean male *pitx3*-cre$^{+/-}$ mice (gene expressed only in the midbrain dopaminergic neurons) resulted in reduced reward-seeking behaviour despite enhanced

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dopaminergic activity that would otherwise increase the motivation to seek food (Kooij et al., 2023). This increase in dopamine signalling pathways remains unexplained, necessitating future investigations.

These studies suggest that reduction in food intake during GLP-1RA treatment is primarily driven by central GLP-1Rs, particularly within the glutamatergic neurons, which contributes to the overall weight loss effect. As shown in Jeromson et al.'s study, the anorectic effect of GLP-1RAs does not sustain, and food intake increases compared to vehicle-treated mice once treatment is stopped (Jeromson et al., 2025). An increase in energy intake might quickly lead to a positive energy balance and, therefore weight regain. Data from these studies are summarized in Table 1.

Clinical studies. GLP-1RA administration in clinical trials has consistently demonstrated a reduction in appetite, supporting the central role of GLP-1RAs in appetite regulation. In individuals with obesity 5 weeks of liraglutide treatment (1.8 or 3.0 mg/day) resulted in a 16% decrease in energy intake as well as reduced hunger and increased feelings of satiety and fullness, indicating a rapid effect on appetite control that aligns with early weight loss (van Can et al., 2014). Similar findings were reported in individuals with T2DM, where liraglutide (once daily titrated to 1.8 mg for 4 weeks) reduced pre-meal hunger compared with both placebo and glimepiride, suggesting appetite suppression beyond improved glycaemic control (Horowitz et al., 2012). However, hormonal changes were less consistent in these investigations. Liraglutide treatment was associated with paradoxical reduction in circulating PYY levels, whereas ghrelin and GIP remained unchanged in individuals with obesity (Horowitz et al., 2012). This highlights a potential dissociation between feelings of fullness and classical gut-derived satiety signals. In contrast, liraglutide treatment (once daily titrated to 3.0 mg for 16 weeks) in adults with non-diabetic obesity increased post-prandial PYY levels while simultaneously reducing food consumption, desire to eat and maximum tolerated gastric volume (Kadouh et al., 2019). These contrary findings potentially can be accounted for by the differences in study design, treatment duration or metabolic status of the participants. Together, these studies indicate that GLP-1RAs reduce subjective appetite outcomes, whereas changes in appetite-regulating hormones are more variable and may not be required for the anorectic effect of GLP-1.

It may be possible that hormone levels adapt during treatment, which makes it difficult to determine hormonal fluctuation and regulation. The role of GLP-1RAs in appetite regulation becomes particularly relevant during weight loss maintenance, a period characterized by increases in hunger and hormonal adaptation favouring weight regain. A long-term randomized controlled trial in adults with non-diabetic obesity demonstrated that low-dose liraglutide (once daily titrated to 1.2 mg/day) administered after a diet-induced 12% weight loss improved weight maintenance over 52 weeks (Iepsen et al., 2015). This effect was accompanied by a smaller decline in GLP-1 and leptin levels, and enhanced postprandial PYY compared with controls, suggesting that GLP-1RA treatment partially counteracts the hormonal adaptation usually associated with weight loss. Particularly, the group receiving GLP-1RAs during the maintenance phase required fewer meal replacements and was associated with greater weight loss, supporting sustained effects on appetite regulation rather than EE alone. Collectively, findings suggest that GLP-1RAs primarily act through central appetite control mechanisms, with hormonal adaptations potentially contributing to long-term weight maintenance rather than driving the initial anorectic response. Because no clinical study yet has evaluated appetite and regulating hormones after GLP-1RA cessation, it remains unknown how these hormone levels will evolve after treatment cessation. Data from these studies are summarized in Table 2.

Preclinical and clinical studies indicate that weight loss induced by GLP-1RAs is accompanied by metabolic adaptations affecting EE, substrate utilization and appetite regulation. Across species, the decrease in EE appears to be primarily driven by reductions in body weight, lean mass and caloric intake, rather than an independent effect of GLP-1RAs on glucose regulation. Reported shifts in substrate utilization towards increased fat oxidation are heterogeneous. Study differences in feeding behaviour, treatment duration, population and methodological approaches make it difficult to study the direct effects of GLP-1RAs on metabolic adaptations, energy intake and weight loss. There are still no clear mechanisms linking GLP-1RAs directly to metabolic adaptations. Additionally, it is still unknown if treatment discontinuation would lead to further metabolic adaptations that could explain the rebound effect. Future studies evaluating metabolic adaptations after treatment withdrawal will be critical to determine the role of GLP-1RAs in the rebound effect, especially measurements of hormonal changes while individuals experience weight regain to pinpoint potential hormone candidates that may be at the pinnacle of increasing body weight.

Functional implications of losing lean and fat mass

Although metabolic adaptations provide important information on how GLP-1RA treatment and cessation affect energy balance, it is unclear whether the effects

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observed are driven by overall weight loss or by specific changes in body composition. Reductions in body weight during weight loss interventions can result from fat or lean mass loss, each carrying different metabolic and functional implications. Moreover, there may be mechanisms underlying changes in losing fat and lean mass that may help to understand how individuals regain weight in absence of GLP-1RA therapies. The following section focuses on how GLP-1RAs affect lean and fat mass loss and how these physiological changes could predict or prevent weight regain.

Lean mass loss. Skeletal muscle is one of the main contributors to resting EE as it corresponds to ∼40% of human body weight and is responsible for ∼30% of the resting EE (Frampton et al., 2020). A loss of muscle mass might cause a decrease in EE. GLP-1RA treatment can lead to lean mass loss in both rodents (Nunn et al., 2024) and humans (Karakasis et al., 2025), but whether GLP-1RAs are detrimental or beneficial to skeletal muscle remains debated. In 2025 an in-depth review of the effect of GLP-1RAs on muscle mass shows that GLP-1RA treatment leads to a 15%–20% body weight loss where lean mass accounts for 20%–50% of total weight loss within the first 3–6 months of treatment. Across both preclinical and clinical studies, lean mass reduction seems to be driven by weight loss, and muscle function is preserved. Although muscle volume decreases with weight loss, this appears to improve muscle quality as there is reduced muscle lipid infiltration (Ceasovschih et al., 2025). The following section aims to extend upon these reported findings by highlighting new work on the effects of GLP-1RAs on skeletal muscle.

Preclinical studies. Preclinical studies suggest that the effects of GLP-1RAs on skeletal muscle are highly context dependent and therefore differ between models of muscle injury or atrophy and weight loss. It should be noted that the GLP-1R is not expressed in skeletal muscle (Hammoud & Drucker, 2023), and these effects that we describe here represent an indirect mechanism, presumably driven by overall body weight loss.

Interestingly, GLP-1RA treatment poses benefits to muscle-related outcomes. In multiple rat models of muscle injury and atrophy, liraglutide (200 μg/kg, 12 h to 14 days of exposure, dependent on injury model) improved muscle regeneration and grip strength in a freeze injury model, preserved muscle mass and enhanced toe spread in a denervation injury model, increased lean mass and grip strength after dexamethasone treatment and mitigated muscle atrophy in an ovariectomy-induced sarcopenia model (Gurjar et al., 2020). These findings support the role of GLP-1RA treatment in promoting muscle maintenance and recovery independent of weight loss.

In contrast, when GLP-1RAs are used primarily to induce weight loss, reduction in lean mass is almost inevitable and mirrors those observed with caloric restriction. Four weeks of either semaglutide (increased to 10 nmol/kg) or pair feeding in adult obese male C57BL/6J mice resulted in a ∼6% reduction in lean mass, reflected in a decrease in multiple muscle weights (triceps, quadriceps, gastrocnemius, soleus, tibialis anterior and extensor digitorum longus) and was accompanied by reduced grip strength (Jeromson et al., 2025). Interestingly, muscle glycogen content was preserved, whereas triglyceride levels decreased in both semaglutide-treated and pair-fed groups, suggesting a consequence of weight loss rather than a drug-specific effect. Moreover semaglutide induced an upregulation of genes associated with protein synthesis, muscle growth and atrophy, suggesting a compensatory mechanism to limit muscle loss. Consistent with this hypothesis, cessation of semaglutide for 5 weeks led to the recovery of muscle mass to levels comparable to vehicle-treated mice (Jeromson et al., 2025). However, the absence of transcriptomic data during the withdrawal phase limits conclusions regarding the persistence or resolution of these molecular adaptations. In contrast, another preclinical study in male diet-induced obesity (DIO) mice after the same treatment regimen (semaglutide, 10 nmol/kg for 28 days) reported that although lean body mass decreased, relative muscle mass and body composition improved (Langer et al., 2026). Whereas small decreases in absolute muscle mass and grip strength were observed, relative grip strength and endurance capacity were enhanced, as semaglutide-treated mice exhibited greater fatigue resistance and running performance comparable to lean control mice. These findings suggest that the observed reduction in absolute lean mass may simply be proportional to overall weight loss although the muscle seems to benefit from treatment as its function and quality are restored.

Preclinical studies suggest that GLP-1RA- associated lean mass loss during treatment is likely driven by weight loss and does not appear to affect muscle function and quality. Although decreases in muscle mass may theoretically contribute to lower EE, the proportion of lean mass loss is modest relative to fat mass reduction. Upon treatment discontinuation lean mass loss seems to be recovered, likely due to an increase in total body weight rather than lean mass acting as a primary driver of weight regain. Nonetheless, preserving skeletal muscle quality and function during weight loss and regain is important to consider due to the role of muscle mass in maintaining physical function and metabolic health. Considering that muscle function and strength worsen with age, it would also be relevant to assess the effects of GLP-1RAs in preclinical models of ageing.

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Clinical studies. Semaglutide lowers body weight primarily through the loss of adipose tissue, with more variable effects on lean mass. In a 24-week retrospective analysis of patients with T2DM, oral semaglutide (dose increased to 14 mg daily) reduced whole-body fat by ∼2.8 kg, without changes in whole-body lean mass or skeletal muscle index (Uchiyama et al., 2023). 88 adults with obesity and T2DM assessed for 24 weeks in a quasi-experimental retrospective study showed ∼8 kg of fat mass loss after semaglutide was administered either orally (dose increased to 14 mg) with 0.7 kg of lean mass loss (8.75% of total weight loss) or subcutaneously (dose increased to 1 mg) with ∼1.7 kg (20% of total weight loss) of lean mass loss (Rodríguez Jiménez et al., 2024). These findings imply different weight loss outcomes with varied administration routes. Liraglutide (increased to 3 mg/day for 10 months) treatment in adults with overweight or obesity resulted in ∼2.7 kg of lean mass loss (23% of total weight loss), with no differences between men and women (Santini et al., 2023). Liraglutide (1.8 mg/day) administration for 26 weeks to patients with T2DM resulted in 2.1 kg (49% of total weight loss) of lean mass loss after 4 weeks of treatment (Eyk et al., 2020). Interestingly, the decrease in resting energy expenditure (REE) with this administration of liraglutide cannot be explained by the loss of lean mass as REE remained reduced after normalization to lean mass. At later stages of treatment (12 and 26 weeks), REE reduction was no longer significant after adjustment for lean mass, suggesting that the longer-term effect on EE may depend on changes in body composition. Conversely, 16 weeks of treatment with liraglutide (increased to 3 mg/day) in adults with overweight and obesity and no T2DM did not change lean mass (Kadouh et al., 2019). Moreover, the impact of liraglutide on body composition appears to be modulated by lifestyle interventions. In a randomized, placebo-controlled trial in adults with obesity without T2DM, liraglutide (3.0 mg/day) administered for a year along with a structured exercise programme after an initial low-calorie diet resulted in greater body fat mass loss while preserving lean mass (Lundgren et al., 2021).

Although GLP-1RA treatment has been associated with reductions in lean body mass, it is important to distinguish lean and muscle mass as well as absolute and relative changes in muscle mass during weight loss. In the context of substantial body weight reduction, decreases in absolute lean mass are expected because patients have a lower total body weight. Therefore, it is important to study lean and muscle mass relative to body weight. Emerging clinical evidence suggests that the reduction in muscle mass may not indicate detrimental effects on muscle quality or function. A proof-of-concept clinical trial in patients with obesity and T2DM treated with semaglutide (increased up to 1 mg/week in the first 4 weeks and then maintained for an additional 12 weeks) demonstrated that although lean body mass and muscle cross-sectional area decreased, the proportion of lean mass relative to body weight increased, indicating an overall improvement in body composition (Langer et al., 2026). Moreover, neither absolute nor relative measures of muscle strengths were impaired despite reductions in muscle size. It is also important to remember that lean mass encompasses all non-fat mass and, therefore differs from muscle mass. These findings suggest that GLP-1RA-associated decreases in lean mass may not in reality reflect meaningful muscle dysfunction or loss of muscle quality.

These studies indicate that GLP-1RA treatment is often associated with lean mass loss, but the amount of change is not consistent between studies perhaps due to the modality of administration. Additionally, it seems like lean mass loss is simply proportional to weight loss and that muscle quality is not affected by treatment. Nevertheless, implementing exercise in combination with GLP-1RA treatment may still be beneficial to preserve skeletal muscle mass and function and preserve EE. Furthermore, the age of the participants and the quality of muscle health at the start of the weight loss treatment may have important implications on lean mass and whole-body physiology. Therefore, more studies focused on elderly population and patients with sarcopenia should be conducted.

Fat mass loss. GLP-1RA induces a greater amount of fat mass loss than lean mass loss (Langer et al., 2026). This raises the question of the importance of fat mass loss during weight loss and what happens to adipose tissue during weight regain. Adipose tissue changes during periods of weight gain and loss, and disruption of its functions can create major challenges for long-term weight maintenance. Understanding adipose tissue characteristics such as fat distribution, adipocyte size, inflammation and metabolic activity may help predict susceptibility to weight regain. This perspective is valuable because healthy adipose tissue contributes to the body's ability to store fat, minimizing lipid spillover to the liver and regulating insulin sensitivity. MacLean et al. (2015) have reviewed the role of adipose tissue in weight regain without the context of GLP-1RAs. Here, we highlight recent studies on GLP-1RA-induced weight loss effects on adipose tissue function and potential mechanisms to promote weight regain.

Preclinical studies. Preclinical studies show that GLP-1RA treatment induces changes in both the brown and the white adipose tissue beyond absolute fat mass loss. In DIO male C57BL/6J mice, semaglutide treatment (30 nmol/kg/day injected intraperitoneally for 12 weeks) reduced visceral fat mass and improved glucose tolerance (Zhu & Chen, 2023). Additionally, adipocytes

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in the epididymal white adipose tissue (eWAT) and the brown adipose tissue (BAT) decreased in size along with the downregulation of proteins involved in lipid uptake, storage and lipolysis such as CD36, FABP5, LPL PLIN2 and ANGPTL4. Consistent with these findings, semaglutide (40 μg/kg every 3 days for 4 weeks, subcutaneously) administration reduced eWAT and subcutaneous WAT mass in obese mice, decreased adipocyte hypertrophy and lowered macrophage infiltration, proinflammatory cytokine expression and endoplasmic reticulum stress in eWAT (Martins et al., 2022b). In the subcutaneous WAT, semaglutide enhanced tissue browning, mitochondrial biogenesis, and upregulation of thermogenic and oxidative genes, while increasing *Lpl* gene expression and reducing lipolysis. Moreover, liraglutide (200 μg/kg/day for 12 weeks) treatment in obese male C57BL/6J mice induced more brown-like signatures in the eWAT such as *Ucp1* and *Prdm16* and microRNAs such as miR186a and miR-378a (Zhao et al., 2024). Furthermore, 12-h treatment of intracerebroventricular liraglutide (3 μg/mouse) in lean male Swiss mice increased BAT temperature (Beiroa et al., 2014), and 24 h after treatment, lean mice had smaller lipid droplets and increased thermogenic proteins like UCP1 and PRDM16 in their BAT. Because GLP-1Rs are absent in WAT and BAT, GLP-1RAs may act indirectly via the sympathetic nervous system as injection of liraglutide in the hypothalamic ventromedial nucleus (VMH) (5 μg/rat) increased BAT UCP1 protein in Sprague–Dawley rats. This suggests that GLP-1RAs may induce weight loss via central appetite suppression and VMH-mediated AMP-activated protein kinase (AMPK) inhibition, increasing UCP1 protein expression in WAT and BAT, and thereby increasing EE. Recently, a study directly compared semaglutide-induced weight loss (0.04 mg/kg/day for 20 days injected subcutaneously) and vertical sleeve gastrectomy in obese mice using single-nucleus RNA sequencing and examined WAT remodelling across multiple cell types (Emont et al., 2025). Despite similar early metabolic improvements, semaglutide-treated mice had reduced inflammatory signalling, increased differentiation in the eWAT, thermogenic adipocytes in the subcutaneous depots and adipocyte gene expression related to obesity despite weight loss compared to those that underwent bariatric surgery. Semaglutide might promote a healthier adipose profile than surgery by reducing inflammation and increasing thermogenesis, though it may retain a molecular memory of the prior obese state which could have implications in long-term weight maintenance. The concept of 'memory of obesity' has been identified in other weight loss interventions, and recent research suggests that adipose tissue retains an epigenetic retention after weight loss. In a multi-omics study, Hinte et al. (2024) found that genes involved in fatty acid metabolism remain suppressed, whereas inflammatory and extracellular matrix remodelling pathways stayed active in both mice and humans after diet-induced weight loss (Hinte et al., 2024). These persistent transcriptional and chromatin changes were associated with accelerated weight regain and larger fat depots, suggesting an important role of epigenetic mechanisms that sustain adipose tissue obesogenic memory during periods of weight loss and maintenance. The state of obesity could therefore contribute to weight regain observed after treatment cessation. Although the availability of studies describing the memory of obesity during and after GLP-1RA treatment is limited, a study from 2025 identified the combination of GLP-1 and dexamethasone (synthetic glucocorticoid that acts as an immunosuppressant inhibiting T cells and pro-inflammatory cytokines) to be effective in reducing immune markers associated with obesogenic memory (i.e. *Ccl2*), and GLP-1 and dexamethasone alone were ineffective (Léon et al., 2025). Although this combination might have some promising prospectives for the weight regain trajectory, this study did not focus on cessation period of this combination therapy. However, considering the role of dexamethasone in impairing CD4+ T cells (Giles et al., 2018) and the fact that CD4+ cells have been associated with obesogenic memory and weight regain (Zou et al., 2018), it is possible that GLP-1/dexamethasone might mitigate weight regain through the resolution of immune obesogenic memory.

Clinical studies. GLP-1RA administration induces weight and fat mass loss, specifically from metabolically unhealthy adipose tissue depots like the visceral adipose tissue. In the prospective SEMALEAN study, semaglutide treatment (increased to 2.4 mg/week for 12 months) in patients with obesity led to sustained fat mass loss (−14% at 7 months and −18% at 12 months), whereas lean mass decreased modestly (∼5%) from baseline to 7 months and then stabilized between 7 and 12 months (Alissou et al., 2026). Among adipose tissue depots, visceral fat mass, a depot associated with unhealthy obesity, appears to be preferentially lost during GLP-1RA therapy (Reinisch et al., 2025). In adults with overweight or obesity without T2DM but at high cardiovascular risk, liraglutide (3.0 mg/day for 40 weeks) combined with reduced calorie diet and increased physical activity resulted in lower visceral adipose tissue (−12.5%) compared to placebo (−1.6%) (Neeland et al., 2021). Moreover, in individuals with obesity and prediabetes or early T2DM, liraglutide (1.8 mg/day until 7% of initial body weight loss) induced greater reduction in visceral fat than lifestyle modification alone, whereas subcutaneous fat loss was comparable between groups (Santilli et al., 2017). In patients with obesity and T2DM, treatment with liraglutide (0.9 mg/day for 24 weeks) reduced visceral and intrahepatic

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fat volume without affecting subcutaneous fat or skeletal muscle, suggesting again an effect on adipose tissue depots associated with metabolic risks (Ishii et al., 2019). A reduction in cardiac adipose tissue has been observed in patients with T2DM treated with liraglutide (1.8 mg/day for 26 weeks). However, these effects do not persist after adjustment for weight loss, suggesting that changes in cardiac fat may be weight dependent (Rasmussen et al., 2021).

GLP-1RA-induced fat loss is accompanied by improvements in adipose tissue function. In patients with non-alcoholic steatohepatitis and overweight or obesity with or without T2DM, liraglutide (1.8 mg/day for 26 weeks) reduced subcutaneous adipose tissue lipolysis, circulating non-esterified fatty acids and markers of adipose inflammation as well as improved adipose insulin sensitivity (Armstrong et al., 2016). There was no change in supraclavicular BAT despite reduction in EE, arguing against the role of BAT in GLP-1RA-induced weight loss in humans. However, it is possible that the dose or duration of treatment may not be adequate to trigger changes in BAT, and therefore more studies are needed to understand the effects of GLP-1RAs on BAT.

In summary, GLP-1RA-induced weight loss results in distinct and depot-specific changes in body composition that may promote long-term weight maintenance. Reduction in lean mass appears secondary to weight loss, but this slight decrease in skeletal muscle may contribute to reduction in EE, which may indirectly increase the risk of weight regain. However, lean mass loss could be mitigated by lifestyle interventions such as structured exercise plans. Fat mass loss, particularly from visceral and ectopic depots, is associated with improved metabolic health and adipose tissue function. Reduction in body fat mass due to GLP-1RA treatment appears to be weight dependent and targets visceral adipose tissue over subcutaneous adipose tissue. Beyond mass loss, GLP-1RAs may favourably impact insulin sensitivity, inflammation and ER stress. Understanding how the relative loss of lean and fat mass evolve after treatment will be essential to identify mechanisms responsible for weight regain.

Current understanding of weight regain and research gaps. Currently, there is no clear mechanism of weight regain after GLP-1RA treatment cessation. Because weight regain is not unique to GLP-1RA-induced weight loss (Marlatt et al., 2017; Noria et al., 2023), it is possible that mechanisms overlap between interventions. Based upon knowledge gained from other weight loss intervention studies, we can hypothesize on what could lead to weight regain. Figures 1 and 2 highlight the potential mechanisms of weight regain in preclinical and clinical models, respectively.

There are a variety of factors that may contribute to mechanisms of weight regain after GLP-1RA-based therapies. First, GLP-1RAs suppress energy intake, which allows for weight loss, but this anorectic effect does not persist after cessation. Second, EE may remain low during GLP-1RA-induced weight loss, which may increase the likeliness of weight regain once appetite returns during treatment withdrawal. Third, while appetite and associated regulating hormones are still limited in the study of GLP-1RA weight loss and regain, but studies on caloric restriction suggest that increased ghrelin and reduced amylin and GLP-1 may be driving factors. Additionally, although GLP-1RAs are known to slow gastric emptying during treatment, an acceleration after discontinuation could potentially increase appetite and food intake, thereby contributing to a positive energy balance and weight regain. In support of this idea, Gonzalez-Izundegui et al. (2021) reported that faster gastric emptying is associated with increased appetite (Gonzalez-Izundegui et al., 2021). Fourth, during weight loss, lipid oxidation is favoured, but once treatment stops, metabolism may shift towards lipid storage by reducing lipolysis and increasing lipid uptake. Moreover, although the reduced size of adipocytes observed with GLP-1RAs could be considered metabolically healthy, in situations such as overfeeding, this may impair the expandability of the adipose tissue and in turn affect their ability to store lipids without inducing lipid spillover (White et al., 2022). On the contrary, in some situations after interventions of caloric restriction, adipocytes become larger when normal food intake occurs, and this positively correlates with increased insulin resistance, which in turns correlates with weight regain (Qiao et al., 2022). With the hypothesis that GLP-1RA cessation promotes fat accumulation, comparable adipose tissue remodelling may contribute to weight regain, but these mechanisms remain to be elucidated.

A key challenge remaining is to distinguish adaptations driven directly by GLP-1RAs from those general consequences of weight loss. A limitation of the current literature is the lack of studies specifically designed to look at the period after treatment cessation. Most studies focus on outcomes during active treatment making it difficult to determine which adaptations persist, which reverse or contribute to weight regain once GLP-1RAs are stopped. Future studies should therefore focus on the withdrawal phase and adapt their design to allow for the identification of GLP-1RA-specific effects. Pair-feeding approaches in preclinical models and calorie-matched controls in clinical trials can help identify caloric-independent effects of GLP-1 RA treatment. Inclusions of appropriate control groups may help determine whether changes reflect a normalization towards a healthier phenotype or a response that promotes weight regain.

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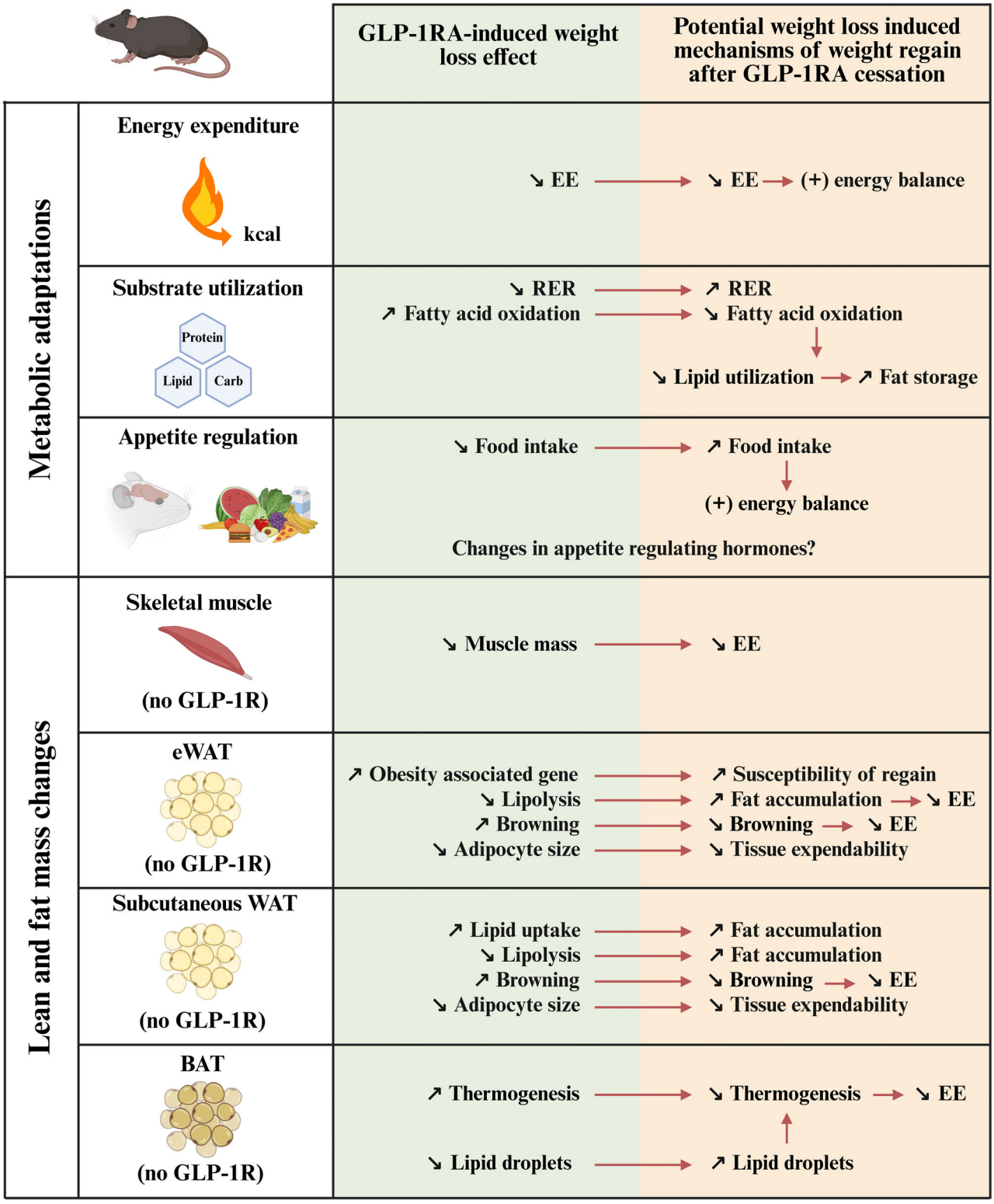

Figure 1. Schematic summary of GLP-1RA-induced weight loss and proposed mechanisms of weight regain after treatment cessation in preclinical models
This figure summarizes metabolic adaptations and fat and lean mass changes associated with GLP-1RA-induced weight loss (left panel) and the proposed mechanisms contributing to positive energy balance and weight regain (right panel) Abbreviations: BAT: brown adipose tissue, EE: energy expenditure, eWAT: epididymal white adipose tissue, GLP-1R: glucagon-like peptide-1 receptor, GLP-1RA: glucagon-like peptide-1 receptor agonist, RER: respiratory exchange ratio, WAT: white adipose tissue.

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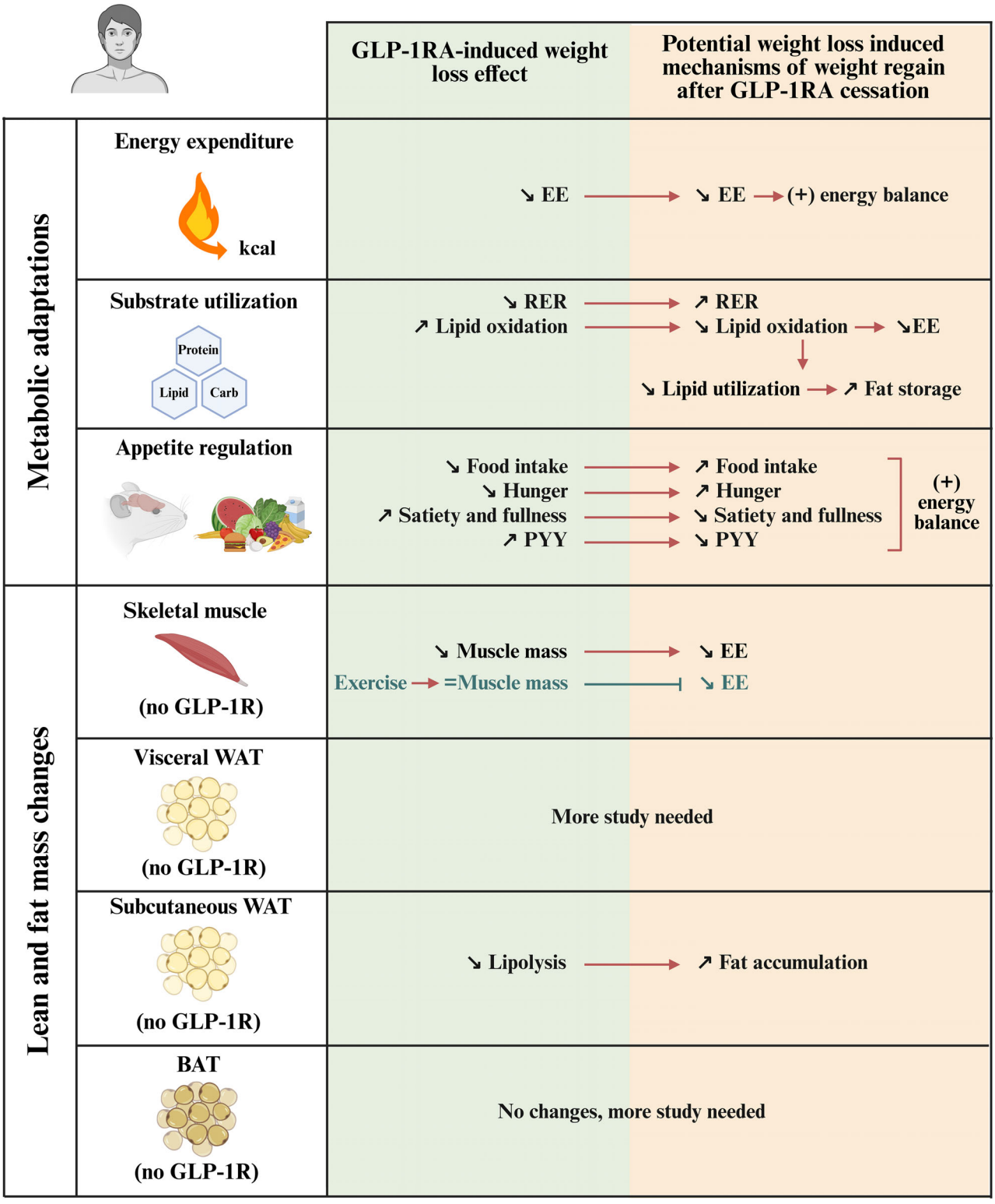

Figure 2. Schematic summary of GLP-1RA-induced weight loss and proposed mechanisms of weight regain after treatment cessation in humans
This figure summarizes metabolic adaptations and fat and lean mass changes associated with GLP-1RA-induced weight loss (left panel) and the proposed mechanisms contributing to positive energy balance and weight regain (right panel). Abbreviations: BAT: brown adipose tissue, EE: energy expenditure, GLP-1R: glucagon-like peptide-1 receptor, GLP-1RA: glucagon-like peptide-1 receptor agonist, RER: respiratory exchange ratio, WAT: white adipose tissue.

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Another gap in the literature concerns the long-term consequences of sustained GLP-1RA treatment. Most studies focus on short- to medium-term treatment periods (ranging from a few weeks in preclinical models to several months in clinical studies), whereas only a limited number has examined prolonged use or post-cessation outcomes. The long-term use of GLP-1RAs has been associated with many protective effects on cardiovascular and renal systems as well as certain risks, including a small increase in risk of cancer (Gamborg et al., 2025), particularly thyroid cancer (Bezin et al., 2023), and gallstone formation (Ramírez-Mejía et al., 2025). These emerging safety concerns suggest that lifelong use may not aways be advised or feasible. In some clinical contexts treatment duration is already limited (e.g. ∼2 years for weight management in UK guidelines; Budini et al., 2026), which gives even more rationale for studying discontinuation of GLP-1RAs. However, because the consequences of treatment cessation remain poorly characterized, it is unclear which GLP-1RA-induced adaptations are transient and reverse after discontinuation and which ones may persist long term. Based on studies focused on cessation (Jeromson et al., 2025; Wilding et al., 2022), it appears that weight loss, reduction in appetite, improved glycaemic control and lean and fat mass loss all rebound after treatment discontinuation, suggesting a lack of persistence of GLP-1RA-induced adaptations. However these studies primarily focused on metabolic end-points and do not address whether the reversal of benefits occurs alongside persistent or lasting changes at the molecular, cellular or neurobiological level.

New GLP-1RA-based therapies – can they mitigate the weight regain? To improve clinical outcomes after GLP-1RA-induced weight loss, new drugs targeting multiple pharmacologic pathways have emerged. These new formulations may contribute to mitigation of weight regain as observed with GLP-1RA administration alone. Figure 3 summarizes how these new therapies may contribute to weight regain mitigation.

Tirzepatide. Tirzepatide, a dual agonist of GIP andGLP-1 receptors, was studied in the 72-week, phase 3 SURMOUNT-1 clinical trial in people with obesity. Treatment with tirzepatide resulted in a greater weight loss than that with GLP-1RA alone (Jastreboff et al., 2022). Tirzepatide administration (3 nmol/kg daily) for 14 days to DIO male mice fed a 50% calorie-restricted diet exhibited decreased EE and increased fat oxidation evident from RER (Ravussin et al., 2025). In the same study men and women with obesity ($n = 55$, aged 18–60 years) received daily injections of tirzepatide for 18 weeks. There was no change in overall EE; however, fat utilization increased during sleep, as reflected by a lower 24-h RER. These studies provide evidence that during weight loss treatment, tirzepatide does not further reduce EE but instead promotes a preference for fat utilization over carbohydrate oxidation. These metabolic changes may offer strategies to reduce weight regain after the cessation of therapy or at least help maintain healthy adipose tissue and skeletal muscle function during periods of weight maintenance. Some studies have started to look at the discontinuation of tirzepatide, and like GLP-1RA mono-

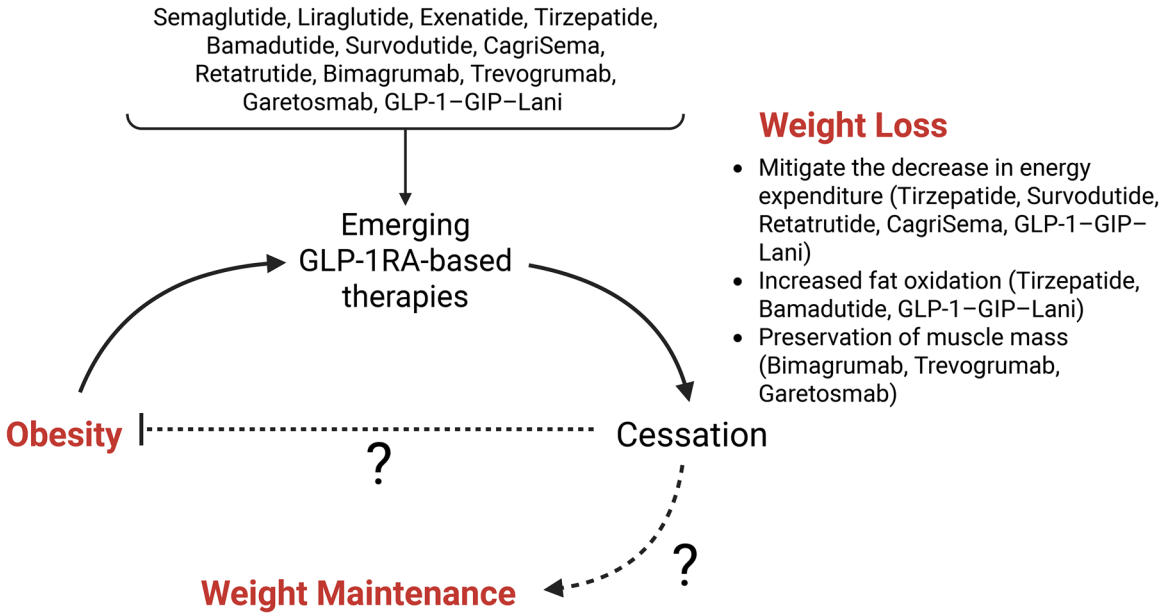

Figure 3. Schematic overview of ways emerging GLP-1RA combination could mitigate weight regain
This figure summarizes the potential benefits of emerging GLP-1RA-based therapies for weight loss and highlights the unresolved question of whether these therapies promote long-term weight maintenance after treatment cessation. GLP-1RA: glucagon-like peptide-1 receptor agonist.

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therapy, weight regain has been reported; 670 patients were treated with tirzepatide for 36 weeks before being randomly assigned to either continue receiving tirzepatide or switch to placebo for 52 weeks. The group that switched to the placebo experienced a 14% weight regain within the 52-week phase and, therefore maintained a 9.9% weight reduction at the end of the study (Aronne et al., 2024). Similarly participants who received tirzepatide for 60 weeks and were then switched to placebo for 52 weeks experienced weight regain, ultimately maintaining a 9.9% weight loss from baseline. In contrast patients who continued tirzepatide throughout the study achieved 21.9% weight loss (Horn et al., 2026). Although the patients are still able to maintain some lost weight, weight regain does occur. Therefore, more studies need to evaluate how this weight regain occurs, and it could be interesting to directly compare GLP-1RA monotherapy with tirzepatide in terms of weight regain outcomes.

Bamadutide and survodutide. Bamadutide (SAR425899), a dual glucagon and GLP-1RA, was found to reduce body composition–adjusted sleeping metabolic rate without affecting the 24-h EE (Corbin et al., 2023). This evidence suggests a selective metabolic adaptation characterized by improved fat oxidation, in contrast to caloric restriction, which typically shifts metabolism away from lipid utilization. However, the exclusive focus on sleeping metabolic rate and the niche nature of this dual agonist may limit the generalizability of these findings to other GLP-1RA formulations and their potential benefits for weight maintenance. Survodutide, another dual agonist of glucagon receptors and GLP-1RAs, has recently emerged with superior outcomes on weight loss in individuals with obesity. In a study on 413 participants (18–75 years) with T2DM, survodutide-treated patients experienced up to −8.7% mean body weight loss, whereas those treated with semaglutide 1.0 mg weekly exhibited only a –5.3% mean body weight loss (Blüher et al., 2024). Although it remains unclear why survodutide leads to greater body weight loss, a few mechanisms have been proposed. First, it may act through liver glucagon receptors and help mitigate the lowering in EE during weight loss (Corbin et al., 2023) as glucagon administration promotes an elevation in EE in both rodents and humans. Furthermore, glucagon receptor agonism may suppress hepatic lipid accumulation (Hayashi, 2021), thereby secreting hormones such as fibroblast growth factor 21, improving sympathetic nervous system regulation and healthy adipose tissue storage. The combination of GLP-1RAs with agonizing the glucagon receptor may provide the necessary change in machinery to drive effective weight loss while allowing individuals to remodel dysfunctional metabolic circuits and maintain lower weight during treatment cessation. Two ongoing phase 3 trials are currently investigating the safety and efficacy of survodutide in patients with obesity and with T2DM (SYNCHRONIZE-2) or without T2DM (SYNCHRONIZE-1) (le Roux et al., 2026; Wharton et al., 2026). Additionally, the SYNCHRONIZE-CVOT selected patients with overweight or obesity and increased cardiovascular risk to determine whether survodutide treatment is associated with improved or worse cardiovascular health by studying major adverse cardiovascular events and blood pressure (Platz et al., 2026). These trials will help define the effects of survodutide treatment. However, to the best of our knowledge, no study has yet evaluated the cessation of that medication. These studies in rodents and humans are required to fully capture these mechanisms and determine its effects on weight regain.

Retatrutide. Considering the effects of tirzepatide and survodutide, it is important to recognize retatrutide, the triple agonist of the GIP, glucagon and GLP-1 receptors. Daily subcutaneous injections of a placebo or retatrutide were administered to 338 individuals with overweight or obesity (18–75 years old) for 48 weeks. After treatment the high-dose (12 mg) retatrutide group experienced a 24.2% reduction in total body weight, compared with a 2.1% reduction in the placebo group (Jastreboff et al., 2023). These findings demonstrate more rapid and greater weight loss than GLP-1RA therapy alone, although the mechanisms underlying retatrutide's effects remain unclear. The known actions of GIP receptor agonism, such as increased fat oxidation (Ravussin et al., 2025), and glucagon receptor agonism, including elevated hepatic glucose production, enhanced lipolysis, suppressed hepatic lipid accumulation (Hayashi, 2021) and increased EE (Wan et al., 2024), possibly work synergistically with the benefits of GLP-1RAs. Together, these mechanisms act on multiple interacting systems to remodel metabolism and promote greater weight loss. As with other formulations it remains unclear whether weight regain occurs after treatment discontinuation. The total weight lost or the rate of loss may influence regain, but this has not yet been systematically studied.

GLP-1R–GIPR–PPAR$\alpha/\gamma/\delta$ quintuple agonism (GLP-1–GIP–Lani). Recent work has introduced a GLP-1R–GIPR–PPAR$\alpha/\gamma/\delta$ quintuple agonist, combining incretin and PPAR signalling (Liskiewicz et al., 2026). PPARα, PPARγ and PPARδ have been independently associated with improvements in lipid and glucose metabolism, insulin sensitivity, adipose tissue remodelling, inflammation reduction and energy balance (Tyagi et al., 2011). A preclinical study has assessed the effects of GLP-1–GIP–Lani (10 nmol/kg/day) in DIO C57BL6/J male mice, which revealed greater weight and fat mass loss and reduction in food intake

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than semaglutide and the dual GLP-1R/GIPR agonist. GLP-1–GIP–Lani further improved glucose tolerance, insulin sensitivity and liver health (Liskiewicz et al., 2026). Although these findings remain preclinical, this new quintuple agonist seems to outperform mono and dual agonism therapies. Whether such multireceptor agonist therapy is a more durable weight loss strategy for humans with obesity and T2DM and mitigates weight regain remains to be elucidated.

CagriSema. Another new emerging GLP-1RA-based therapy for weight loss is the combination of semaglutide and cagrilintide, an amylin analogue, known as CagriSema. The REDEFINE 1 trial assessed CagriSema *versus* cagrilintide, semaglutide and placebo in 3,417 adults with overweight or obesity without T2DM. After 68 weeks of treatment, the cagrilintide–semaglutide group lost 20.4% of body weight, compared with 3%, 11.5% and 14.9% in the placebo, cagrilintide and semaglutide groups, respectively (Garvey et al., 2025). Data from that same trial revealed that CagriSema further reduced blood pressure compared to semaglutide and cagrilintide alone (Verma et al., 2026). The REIMAGINE 3 trial assessed the effects of CagriSema in individuals with T2DM (Rosenstock et al., 2026). Both treatment doses (1.0 and 2.4 mg) improved glycaemic control and induced substantial weight loss compared to placebo. After 40 weeks of treatment, body weight decreased by up to 12% and HbA1c decreased by up to 2.33 percentage points. As a satiating hormone that allows decreased food intake, amylin is known to slow down gastric emptying and inhibit glucagon release (Lutz et al., 1995; Lutz, 2022). Additionally, amylin prevents a decrease in EE expected during weight loss periods in rats (Wielinga et al., 2010), which could help prevent weight regain. Again, treatment with CagriSema in patients with obesity and T2DM may induce an effective weight loss that may realign long-term health outcomes by reducing lower EE during weight loss and may provide added benefits to appetite-regulating hormones. This suggests a potential strategy to reduce weight regain and maintain metabolic health after stopping treatment; however further investigation is warranted.

Bimagrumab, trevogrumab and garetosmab. The strategy to preserve skeletal muscle mass during weight loss is of great interest in novel pharmacotherapies (Hopkins, Gibbons and et al. 2023). Bimagrumab, a monoclonal antibody against activin II receptors, in combination with semaglutide exhibited a greater fat mass loss and a preserved lean mass in DIO mice compared to those that were treated with semaglutide alone (Nunn et al., 2024). A recent study showed that human antibodies targeting growth differentiation factor 8 (trevogrumab) and activin A (garetosmab) modulate activin type II A and B receptors, increasing muscle mass and reducing fat mass in non-human primates (Mastaitis et al., 2025). A phase 2 trial in adults with obesity has assessed the effects of different doses of semaglutide, bimagrumab and the combination of both treatments for 48 weeks (Heymsfield et al., 2026). The combination of bimagrumab and semaglutide induced greater weight loss than either agent alone, resulting in up to 20.2% body weight reduction at 48 weeks due to important reduction in fat mass and visceral adipose tissue since lean mass was preserved. Additionally, this combination therapy was associated with improvement in cardiometabolic parameters, including reductions in fasting insulin, diastolic blood pressure and high-sensitivity C-reactive protein (marker of low-grade systemic inflammation). These findings demonstrate that preclinical findings on the combination of bimagrumab and semaglutide translate into clinical data, making this treatment a promising weight loss option. To the best of our knowledge, no study has evaluated the impact of these new drugs on EE in humans. However, improvements in muscle mass observed with these treatments may help preserve lean mass during weight loss and, consequently, may reduce the risk of weight regain after treatment cessation. Despite this, the health of adipose tissue during weight loss induced by these therapies has not been examined. Therefore, future studies investigating the effects of treatment discontinuation will be important to determine the potential for sustained weight maintenance when therapies promote both muscle mass gain and fat mass loss.

Conclusion

This review highlights the metabolic and physiological responses to GLP-1RA-induced weight loss and assesses the potential of emerging GLP-1-based therapies on weight maintenance. It seems that weight loss induces several adaptations, including reduction in EE and appetite. It is difficult to find which changes are GLP-1RA dependent. The composition of the weight loss and subsequent weight regain might also influence long-term metabolic health and weight maintenance and, therefore warrants further investigation. Currently, there is inadequate information to understand the mechanisms behind the rebound effect after GLP-1RA cessation. More research is necessary to distinguish the drug-specific effects from the other factors like food intake that play a role in weight loss and subsequent regain. Although newer drugs seem promising in the context of weight maintenance, their ability remains to be determined.

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Additional information

Competing interests

None declared.

Author contributions

All authors approved the final version of the manuscript, all persons designated as authors qualify for authorship and all those who qualify for authorship are listed. C.E.M.P.: conceptualization, investigation, visualization, writing – original draft and writing – review and editing. R.N.: conceptualization, investigation, visualization, writing – original draft and writing – review and editing. J.L.B.: conceptualization, funding acquisition, investigation, project administration, supervision, validation, visualization, writing – original draft and writing – review and editing.

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