GMR
The Original

Molecular and Metabolic Mechanisms Influencing Long-Term Weight Regulation after Discontinuation of GLP-1 Receptor Agonists in Adults with Obesity in Saudi Arabia

Faisal F. Alshehri[1], Waleed Khalid Aljasser[1], Mohammed Sultan Alzimami[1], Mousa Mutlaq Almuhanna[1], Mohammad Daham Al Rafedi[2], Waeul Hussain Alsaleh[3],

1 Family Medicine Resident, King Saud Medical City, Riyadh, Saudi Arabia.
2 Family Medicine Resident, Al Aziziyah PHC, Riyadh Health Cluster 1, Riyadh, Saudi Arabia
3 Consultant of Family Medicine, King Fahad Medical City, Riyadh, Saudi Arabia

Corresponding Author: Mda1414@hotmail.com

ABSTRACT

Glucagon-like peptide-1 (GLP-1) receptor agonists have revolutionized obesity management, demonstrating unprecedented weight loss efficacy in clinical trials and real-world settings. However, weight regain following discontinuation represents a significant clinical challenge and a major concern for both patients and healthcare providers. This comprehensive review examines the mechanisms, patterns, and strategies for long-term weight maintenance after discontinuation of GLP-1 receptor agonists in adults with obesity, with specific emphasis on the Saudi Arabian context. A systematic literature search was conducted across multiple databases including PubMed, Scopus, and Google Scholar through January 2026. The review synthesizes evidence on metabolic rebound, hormonal adaptations, behavioral factors, and lifestyle interventions that influence weight maintenance post-discontinuation. Key findings demonstrate that individuals discontinuing GLP-1 receptor agonists experience substantial weight regain, with mean regain of 9.9 kg within the first year for semaglutide and tirzepatide, compared to 2.2 kg for liraglutide, ultimately returning to baseline weight within 1.5-1.7 years. Evidence suggests that weight regain is multifactorial, driven primarily by physiological mechanisms including hormonal adaptations, reduced satiety hormone secretion, increased orexigenic hormone levels, and metabolic adaptation. This review highlights the chronic, relapsing nature of obesity and emphasizes the necessity for continued pharmacological therapy, intensive lifestyle modifications, and behavioral interventions to maintain weight loss achieved during GLP-1 receptor agonist treatment. The review identifies critical research gaps specific to the Saudi Arabian population and provides evidence-based recommendations for clinical practice, healthcare policy, and future research directions.

Keywords: *GLP-1 receptor agonists, weight maintenance, weight regain, obesity management, metabolic adaptation, hormonal changes.*

INTRODUCTION

Obesity: A Chronic Disease of Global and Regional Significance

Obesity has emerged as one of the most pressing public health challenges of the 21st century, affecting millions of individuals worldwide and contributing significantly to premature mortality and reduced quality of life. According to recent epidemiological data, the global prevalence of obesity has nearly tripled since 1975, with the World Health Organization estimating that over 1.9 billion adults worldwide are overweight, and approximately 650 million are classified as obese (Sartorio et al., 2003). The condition extends across all demographic groups, ages, and socioeconomic strata, though disparities exist in prevalence rates based on geography, culture, and development status.

Saudi Arabia presents a particularly concerning epidemiological picture. According to the General Authority for Statistics (GASTAT) 2024 Health Determinants Statistics Publication, the obesity rate among the Saudi population aged 15 years and above stands at 23.1%, with an additional 45.1% classified as overweight (General Authority for Statistics, 2024). Among children aged 2-14 years, the obesity prevalence reaches 14.6%, with 33.3% categorized as overweight (General Authority for Statistics, 2024). These figures represent a consistent upward trend over recent decades, positioning Saudi Arabia among the countries with the highest obesity prevalence globally. Notably, obesity prevalence in Saudi Arabia has increased from approximately 16% among men and 24% among women in 1996 to current levels exceeding 23%, with some regional studies reporting prevalence as high as 35.6% (Almubark et al., 2024). This escalating trend carries substantial economic implications; projections indicate that by 2040, obesity-related conditions in Saudi Arabia will generate an estimated 2.26 million new cases of type 2 diabetes mellitus, chronic liver diseases, and liver cancer among the working-age population, with direct healthcare costs exceeding 127 billion Saudi Riyals (Al-Omar et al., 2024).

Obesity as a Chronic Disease Requiring Long-Term Management

Contemporary medical understanding recognizes obesity not as a behavioral issue or simple matter of willpower, but rather as a chronic, relapsing metabolic disease requiring ongoing therapeutic intervention. This paradigm shift, increasingly accepted by major medical organizations including the American Medical Association, the American Heart Association, and endocrinology societies worldwide, fundamentally changes the approach to obesity treatment. Like other chronic conditions such as hypertension or diabetes mellitus, obesity involves complex physiological dysregulation including abnormal appetite regulation, impaired satiety signaling, hormonal imbalances, and altered energy expenditure (Garvey et al., 2016).

The chronic nature of obesity is evidenced by the remarkable consistency with which individuals regain weight following treatment discontinuation, regardless of the intervention employed. Historical data from behavioral weight loss programs demonstrate that without continued intervention, most individuals regain 33-50% of lost weight within 1 year and typically return to baseline weight within 5 years (Wing & Phelan, 2005). Understanding obesity as a chronic disease has critical implications for clinical practice and patient expectations; it suggests that, analogous to other chronic conditions, ongoing management is necessary to maintain therapeutic gains.

Evolution of Pharmacological Obesity Management and the GLP-1 Receptor Agonist Revolution

The pharmacological management of obesity has evolved substantially over several decades. Prior to 2021, available anti-obesity medications demonstrated modest efficacy, with older agents such as orlistat producing a mean weight loss of approximately 2-3 kg compared to placebo (Yanovski et al., 2014). The introduction of semaglutide in 2021 marked a watershed moment in obesity pharmacotherapy. This high-dose GLP-1 receptor agonist demonstrated unprecedented efficacy, producing mean weight loss of approximately 15 kg in the STEP 1 trial, substantially exceeding previous pharmacological interventions (Wilding et al., 2022).

The mechanism underlying GLP-1 receptor agonist efficacy involves mimicry of the endogenous glucagon-like peptide-1 hormone, a physiologic regulator of appetite, satiety, and glucose homeostasis. GLP-1 receptor agonists enhance postprandial insulin secretion, slow gastric emptying, promote feelings of satiety, and importantly, act on hypothalamic appetite centers to reduce hunger and food cravings (Holst et al., 2009). The class includes agents of varying potency and formulations, with commonly used medications including liraglutide (1.2-3.0 mg weekly), semaglutide (0.5-2.4 mg weekly or 25-50 mg orally daily for newer formulations), dulaglutide, exenatide, and the more recently developed dual GLP-1/GIP receptor agonist tirzepatide (5-15 mg weekly) (Nuffer et al., 2016).

The rapid adoption of GLP-1 receptor agonists has been remarkable, particularly in high-income countries. In Saudi Arabia, adoption has been equally striking; a 2024 cross-sectional study found that semaglutide was the most commonly prescribed GLP-1 receptor agonist (13.7% of surveyed participants), though it also noted that over 54.5% of users discontinued treatment due to shortage or cost, and 42.7% discontinued due to side effects (Alhowiti et al., 2025).

The Critical Knowledge Gap: Weight Regain Following Discontinuation

Despite the remarkable efficacy of GLP-1 receptor agonists during active treatment, a critical and poorly understood challenge emerges upon treatment discontinuation: weight regain. Real-world data suggests that approximately 50% of patients discontinue GLP-1 receptor agonists within 12 months of initiation, with discontinuation rates reaching 64.8% among patients without type 2 diabetes (Long et al., 2024). Discontinuation occurs due to multiple factors including cost, medication shortages, gastrointestinal adverse effects, and patient preference or clinical necessity to cease therapy.

What happens to body weight after GLP-1 receptor agonist discontinuation remained incompletely characterized until very recently. A landmark 2025 meta-analysis and systematic review published in The Lancet and subsequently reported in BMJ examined 36 studies evaluating weight trajectories after discontinuation of anti-obesity medications (West et al., 2026). The findings were striking: across all weight-loss medications, participants regained an average of 4.8 kg in the first year and 6.0 kg with incretin mimetics specifically. For semaglutide and tirzepatide discontinuation, mean weight regain in the first year was 9.9 kg. Using mathematical modeling, the meta-analysis projected that individuals would return to their baseline weight within approximately 1.7 years after discontinuation, with semaglutide and tirzepatide users returning to baseline by approximately 1.5 years (West et al., 2026).

Additionally, cardiometabolic risk factors reverted nearly in parallel to body weight, with systolic blood pressure increasing by 0.5 mm Hg per month, diastolic blood pressure by 0.2 mm Hg per month, fasting plasma glucose increasing 0.05 mmol/mol per month, and triglyceride levels rebounding markedly (West et al., 2026). These findings underscore that discontinuation of GLP-1 receptor agonists does not simply result in weight regain but represents a broader metabolic rebound affecting multiple cardiometabolic parameters.

Rationale for Saudi Arabia-Specific Focus

While weight regain following GLP-1 receptor agonist discontinuation has been extensively studied in high-income Western countries, Saudi Arabia presents unique clinical, epidemiological, and healthcare system contexts that warrant specific investigation. First, obesity prevalence and incidence in Saudi Arabia exceed global averages, creating a larger population potentially affected by discontinuation-related weight regain. Second, the Kingdom faces unique healthcare access and cost issues, with GLP-1 receptor agonists remaining expensive medications with variable insurance coverage and availability (Alhowiti et al., 2025). Third, psychosocial and cultural factors influencing obesity management in Saudi Arabia differ from Western contexts; research has documented associations between obesity, depression, anxiety, and reduced quality of life specific to Saudi populations (Alnasser et al., 2024). Fourth, behavioral factors including

dietary patterns, physical activity levels, and response to behavioral interventions may differ in the Saudi context due to cultural, religious, and socioeconomic factors.

To date, there exists no comprehensive review examining weight maintenance after GLP-1 receptor agonist discontinuation with specific attention to the Saudi Arabian context. This review aims to address this knowledge gap by synthesizing current evidence on mechanisms of weight regain, patterns of weight regain across different GLP-1 receptor agonists, and evidence-based strategies for long-term weight maintenance post-discontinuation, with consideration of factors relevant to Saudi populations.

LITERATURE REVIEW

Epidemiology and Burden of GLP-1 Receptor Agonist Discontinuation

Recent real-world studies have documented remarkably high discontinuation rates for GLP-1 receptor agonists, raising important questions about durability of weight loss in clinical practice. A comprehensive cohort study analyzing 125,474 patients initiating GLP-1 receptor agonists in the United States found that 46.5% of patients with type 2 diabetes discontinued within one year, compared to 64.8% of patients without diabetes (Long et al., 2024). Importantly, discontinuation was significantly associated with greater weight loss, suggesting that patients achieving maximal therapeutic benefit may be at particular risk for discontinuation, whether through patient preference, clinical decision-making, or cost constraints.

A 2024 real-world analysis by Abdel-Bary and colleagues examining over 135,000 patients found that among approximately 37,000 semaglutide users, approximately 2,567 discontinued treatment; six months post-discontinuation, the median weight change was 0%, suggesting considerable heterogeneity in weight regain experiences (Soundararajan & nference Research Team, 2026). This observation contrasts sharply with clinical trial data showing more uniform and rapid weight regain, suggesting that real-world outcomes may differ substantially from controlled trial environments.

In Saudi Arabia specifically, a 2024 cross-sectional study of 481 participants found that 21.8% were using GLP-1 agonists; among those users, 54.5% interrupted their GLP-1 agonist therapy due to shortage or cost, and 42.7% due to side effects (Alhowiti et al., 2025). These findings highlight that discontinuation in the Saudi context is driven substantially by access and cost barriers rather than patient preference alone, a distinction with important clinical implications.

Temporal Patterns of Weight Regain: Evidence from Clinical Trials

The STEP 1 trial extension provided critical data on weight regain following semaglutide discontinuation. In this trial, participants treated with semaglutide 2.4 mg weekly for 68 weeks achieved mean weight loss of approximately 15 kg. Upon discontinuation and entry into a one-year follow-up period, participants regained a mean of 11.6 percentage points of their lost weight by week 120, translating into a net weight loss of only 5.6% from baseline, compared to 0.1% in the placebo group (Wilding et al., 2022). Notably, within the first year of discontinuation, participants regained approximately two-thirds of their weight loss, with the rate of regain being highest immediately following discontinuation.

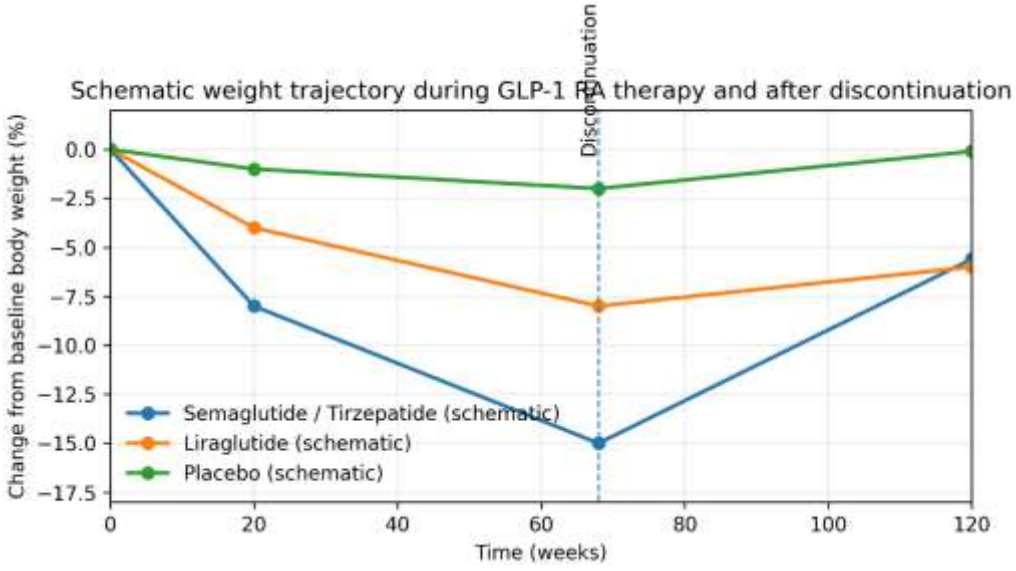
Subsequent meta-analytic evidence has confirmed and extended these observations. A 2025 meta-analysis published in Cureus, examining 36 studies on weight regain after discontinuation of GLP-1 receptor agonists and other anti-obesity drugs, found important differential effects by agent type (Alsayes et al., 2025):

- Semaglutide showed the highest weight regain after discontinuation (mean difference = −5.15 kg; 95% confidence interval [CI]: −5.27 to −5.03)

- Exenatide showed intermediate weight regain (mean difference = −3.06 kg; 95% CI: −3.91 to −2.22)
- Liraglutide showed modest weight regain (mean difference = −1.50 kg; 95% CI: −2.41 to −0.26)
- Orlistat showed modest weight regain (mean difference = −1.66 kg; 95% CI: −2.75 to −0.58) (Alsayes et al., 2025)

These findings suggest a potency-dependent relationship: higher-potency GLP-1 receptor agonists produce greater weight regain upon discontinuation. The differential effects may reflect the mechanism of action; high-potency agents producing substantial appetite suppression may generate stronger adaptive counter-regulatory mechanisms upon discontinuation.

Figure 1. Schematic weight trajectory during GLP-1 receptor agonist therapy and after discontinuation (illustrative).



Mechanisms of Weight Regain: Physiological Basis Beyond Behavioral Factors

A critical insight from contemporary obesity research is that weight regain following treatment discontinuation is fundamentally a physiological phenomenon, not simply a behavioral failure or regression to previous eating habits. Multiple complementary mechanisms drive weight regain.

Hormonal Adaptations and Gut Hormone Changes

Body weight is tightly regulated by hormones from the gastrointestinal tract, pancreas, and adipose tissue that act primarily in the hypothalamus to modulate appetite and satiety. A seminal study by Sumithran and colleagues followed participants through a weight loss intervention and subsequent follow-up period, measuring multiple appetite-regulating hormones (Wilding et al., 2022). At baseline, before weight loss, participants demonstrated certain hormone levels; following approximately 30 kg weight loss over 10 weeks, satiety hormones including leptin, peptide YY (PYY), cholecystokinin (CCK), insulin, and amylin decreased significantly, while the orexigenic hormone ghrelin increased substantially (Alhowiti et al.,

2025). Critically, when participants were reassessed one year later a time when most had regained substantial weight the unfavorable hormone pattern persisted: satiety hormones remained suppressed and ghrelin remained elevated (Sumithran et al., 2011). These persisting hormonal changes directly translate into increased hunger and reduced satiety, creating a powerful physiological drive toward weight regain.

The mechanism underlying these hormonal changes involves both direct effects of reduced adipose tissue mass and adaptive mechanisms that defend against further weight loss. Leptin, produced by adipose tissue, decreases proportionally with reduced fat mass, signaling energy deficit to the hypothalamus. Reductions in GLP-1, PYY, and CCK hormones normally secreted by intestinal L-cells in response to nutrient absorption also occur, reducing satiety signaling. Conversely, ghrelin, the primary orexigenic hormone produced by gastric fundic cells, increases, enhancing hunger and promoting food-seeking behavior (Blundell et al., 2015).

The persistence of these hormonal changes months to years after weight loss suggests that the metabolic "set point" the body's defended weight around which it regulates shifts only slowly or incompletely following weight loss therapy. This has led researchers to propose that the body actively defends against weight loss much as it would defend against starvation, a physiological mechanism that evolved to ensure survival in periods of food scarcity (Fothergill et al., 2016).

Metabolic Adaptation and Reduced Energy Expenditure

In addition to hormonal changes, weight loss triggers "metabolic adaptation," a reduction in resting energy expenditure greater than predicted by changes in body composition alone. This phenomenon was dramatically illustrated in the "Biggest Loser" study, which followed contestants from a televised weight loss competition (Alnasser et al., 2024). At the end of the competition, contestants had achieved substantial weight loss through combined dietary restriction and intensive exercise. However, six years later, despite weight regain, metabolic rate remained suppressed relative to body composition predictions (Yanovski et al., 2014). On average, resting metabolic rate was approximately 500 kcal/day lower than predicted, representing a compensatory response to the sustained energy deficit experienced during weight loss.

The biological basis of metabolic adaptation involves multiple mechanisms: reduced sympathetic nervous system activity, altered thyroid hormone secretion patterns, reduced brown adipose tissue thermogenesis, and decreased uncoupling protein activity in mitochondria (Rosenbaum et al., 2010). Collectively, these changes conserve energy in the face of perceived energy scarcity, a survival mechanism that is maladaptive in the modern environment where energy is abundant.

Upon discontinuation of GLP-1 receptor agonists, metabolic adaptation persists; the reduced resting metabolic rate characteristic of weight loss does not rapidly normalize to match the new, lower body weight. This means that when individuals discontinue GLP-1 receptor agonists and appetite suppression diminishes, they have both increased hunger (from hormonal changes) and lower energy expenditure (from metabolic adaptation), creating a potent combination driving weight regain.

Central Nervous System Changes and Food Reward Circuitry

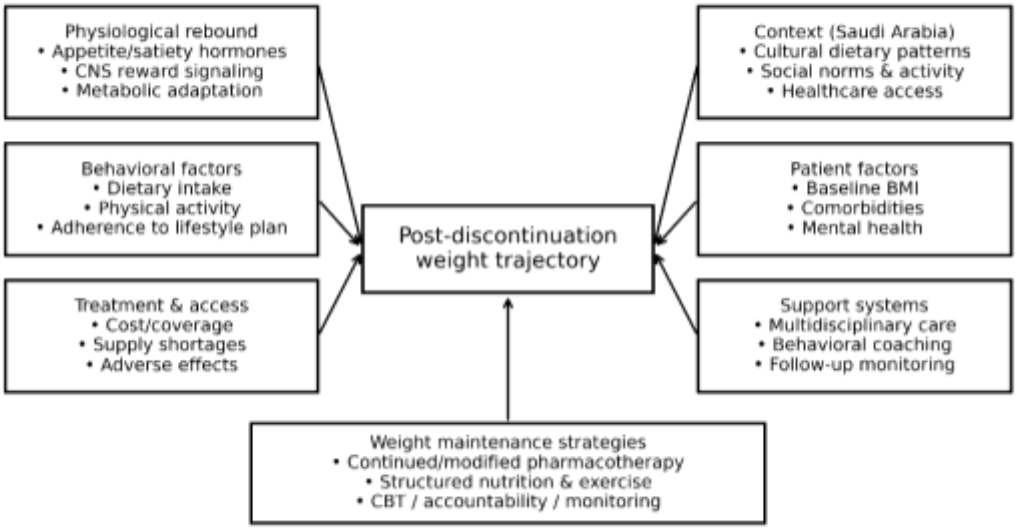
Beyond peripheral hormonal and metabolic changes, weight loss alters neural processing of food reward. Neuroimaging studies demonstrate that individuals with obesity show altered reward processing in response to food cues relative to healthy-weight controls, with hyperactivation of brain regions involved in reward, motivation, and cue-reactivity (Volkow et al., 2008). This hyper-responsiveness to food cues is hypothesized to contribute to excess food intake and weight gain.

Importantly, weight loss may not fully normalize reward-driven eating; individuals who have lost weight may continue to show heightened reward responses to high-calorie foods despite reduced appetite from

GLP-1 receptor agonism (Volkow et al., 2008). Upon discontinuation of GLP-1 receptor agonists, these reward circuits, combined with the hormonal and metabolic changes described above, may collectively drive increased food intake and weight regain.

Discontinuation and Weight Regain: The Clinical Reality

Figure 2. Conceptual framework summarizing key drivers and moderators of weight regain after GLP-1 receptor agonist discontinuation, including Saudi Arabia–relevant context factors.



Real-World vs. Trial-Based Outcomes

A critical distinction exists between controlled clinical trial settings and real-world clinical practice regarding weight regain after GLP-1 receptor agonist discontinuation. In randomized controlled trials, discontinuation is typically planned and structured, with participants receiving counseling and monitoring. Furthermore, trial participants often come from higher socioeconomic backgrounds and more motivated populations.

In contrast, real-world discontinuation frequently occurs unexpectedly due to cost, access issues, adverse effects, or patient decision-making. An important real-world analysis by Soundararajan and colleagues at nference, examining 135,000+ patients and over 14 million clinical records, found more favorable weight regain outcomes than clinical trials suggested (Soundararajan & nference Research Team, 2026). Among semaglutide users who discontinued (n=2,567), six months post-discontinuation, approximately 32% had sustained their weight loss and 35% were still losing weight, with only 28% having regained the lost weight (Soundararajan & nference Research Team, 2026). Notably, the median weight change six months post-discontinuation was 0%, suggesting that many patients achieved weight stabilization rather than the dramatic regain observed in trials.

These real-world data suggest that when patients receive exercise guidance and nutritional counseling alongside medication discontinuation, weight regain may be less rapid than clinical trials indicate. This distinction has important implications for clinical practice and patient expectations.

Factors Associated with Weight Regain vs. Weight Maintenance

Recent research has identified factors associated with differential weight regain outcomes. The nference analysis noted that weight regain was associated with anxiety, anemia, thyroid hormone fluctuations (even within normal ranges), depression, and antibiotic prescriptions following discontinuation (Wing & Phelan, 2005). However, the authors emphasized that these associations do not indicate causation and may represent confounding or bidirectional relationships.

One robust finding across multiple studies is that structured behavioral support, exercise guidance, and nutrition counseling substantially reduce weight regain rates. In the real-world analysis, patients who received exercise guidance following discontinuation were nearly twice as likely to sustain their weight loss compared to those who did not receive such guidance (Wilding et al., 2022). This observation aligns with mechanistic understanding; behavioral interventions support weight maintenance through multiple pathways including improved dietary adherence, sustained physical activity (which can enhance postprandial GLP-1 secretion), and psychological support for managing increased hunger and food cravings.

Strategies for Optimizing Weight Maintenance after GLP-1 Receptor Agonist Discontinuation

Lifestyle and Behavioral Interventions

Structured Exercise Programs

Emerging evidence suggests that exercise plays a critical role in weight maintenance following GLP-1 receptor agonist discontinuation. A 2024 study presented at the European Congress on Obesity examined whether lifestyle modifications could prevent weight regain in patients who discontinue GLP-1 receptor agonists (Jensen et al., 2024). The study employed a novel approach: dosage reduction while simultaneously intensifying lifestyle coaching. Among 353 participants who desired to discontinue semaglutide, 240 agreed to a gradual dose taper over 9 weeks while receiving behavioral coaching on diet and exercise. Among the 85 participants followed for 26 weeks after complete dose taper, weight remained remarkably stable, with only an average 1.5% weight loss from discontinuation, substantially superior to the expected 9.9 kg regain seen in trials.

Additionally, a study by Holt and colleagues examining supervised exercise following dietary weight loss found that participants randomized to one year of supervised exercise increased late-phase postprandial GLP-1 response by 25% compared with continued usual activity (Holt et al., 1992). The authors proposed that exercise training itself may enhance the body's endogenous GLP-1 secretion, potentially providing an endogenous appetite-suppressant effect that partially substitutes for the exogenous GLP-1 receptor agonist.

Nutritional Interventions and Dietary Approaches

While dietary interventions alone are insufficient to prevent weight regain after GLP-1 receptor agonist discontinuation, evidence suggests that specific dietary approaches may enhance weight maintenance. A systematic review of dietary interventions for weight management found that low-carbohydrate diets, in particular, may enhance endogenous GLP-1 secretion; in one study, GLP-1 remained stable in individuals consuming low-carbohydrate diets but decreased with low-fat dietary approaches (Gardner et al., 2020). This suggests that a dietary composition emphasizing protein and low glycemic index carbohydrates might enhance satiety and stabilize weight following medication discontinuation.

Importantly, successful long-term weight maintenance appears to require that individuals learn and internalize healthy eating patterns while taking GLP-1 receptor agonists. Former FDA Commissioner David Kessler, commenting on weight regain after GLP-1 discontinuation, noted: "It's not the drugs that lead to lasting weight loss. It ultimately depends on whether individuals learn to modify their eating habits while on those medications" (Soundararajan & nference Research Team, 2026). This perspective emphasizes that GLP-1 receptor agonists should be viewed as tools facilitating behavioral change rather than standalone treatments, and that patients who use medication time to develop sustainable dietary patterns achieve superior outcomes.

Continuation or Modified Pharmacotherapy

Continued GLP-1 Receptor Agonist Therapy

A straightforward but underexplored strategy for preventing weight regain is continuation of GLP-1 receptor agonist therapy, potentially at lower doses. A 2024 study found that lower doses of semaglutide were as effective as higher doses at preventing weight regain in participants who wished to discontinue therapy (Jensen et al., 2024). This finding suggests that dose reduction combined with lifestyle intervention might provide a middle ground between full discontinuation (with associated weight regain) and maintenance of higher doses (with associated costs and side effects).

Evidence for this approach comes from the observation that satiation the sense of fullness during eating can be achieved at lower GLP-1 receptor agonist doses than maximal weight loss, raising the possibility that lower maintenance doses could stabilize weight while reducing medication costs and side effects (Wilding et al., 2021).

Switching to Alternative Anti-Obesity Medications

An emerging strategy for preventing weight regain involves switching from GLP-1 receptor agonists to alternative anti-obesity medications upon discontinuation. One study by Paddu and colleagues found that switching to older anti-obesity medications (metformin, topiramate, bupropion) after 12 months of GLP-1 receptor agonist therapy was effective for maintaining weight loss for two years (Paddu et al., 2024). While these older agents produce modest weight loss individually (typically 2-4 kg), they may help prevent the dramatic regain observed with abrupt discontinuation.

Additionally, newer dual GLP-1/GIP receptor agonists such as tirzepatide represent a complementary rather than alternative pharmacological approach. While tirzepatide demonstrates similar weight regain to semaglutide upon discontinuation, combining GLP-1 receptor agonists with GIP agonism and potentially upcoming triple agonists (combining GLP-1, GIP, and glucagon agonism) may provide additional weight loss and potentially more durable effects, though long-term discontinuation data for these agents remain limited.

Multidisciplinary and Psychological Interventions

Cognitive-Behavioral Therapy and Behavioral Support

Psychological interventions play a critical role in long-term weight maintenance. A comprehensive systematic review of psychological interventions for weight reduction identified 13 distinct psychological intervention types, with cognitive-behavioral therapy (CBT) and motivational interviewing being most commonly studied (Hamer et al., 2024). These interventions address underlying psychological factors including low mood, low self-efficacy, anxiety, body image concerns, and emotional eating factors that contribute to weight regain upon medication discontinuation.

Importantly, individuals with obesity and those who have lost substantial weight show elevated rates of depression and anxiety (Almohannadi et al., 2024; Alnasser et al., 2024). In a Saudi Arabian study examining the relationship between obesity and mental health, 86% of participants perceived obesity as having a negative effect on quality of life and mental health (Alnasser et al., 2024). This psychological burden may intensify upon medication discontinuation, as individuals face both increased hunger and the prospect of regaining weight. Targeted psychological interventions addressing these factors may substantially improve outcomes.

Enhanced Monitoring and Behavioral Accountability

Frequent weight monitoring and behavioral follow-up appear to improve weight maintenance outcomes. A prospective study examining long-term weight loss maintainers found that more frequent self-weighing, regular healthcare provider follow-up, and behavioral accountability were associated with superior long-term outcomes (Phelan et al., 2020). In clinical practice, individuals discontinuing GLP-1 receptor agonists might benefit from structured follow-up visits occurring every 2-4 weeks initially, with measurement of weight and review of dietary and physical activity patterns.

Obesity Management Context in Saudi Arabia: Specific Considerations

Healthcare Access and Medication Cost Barriers

In Saudi Arabia, GLP-1 receptor agonists remain expensive medications with variable insurance coverage. The 2024 Alhowiti study found that over half (54.5%) of GLP-1 agonist users interrupted treatment due to shortage or cost, representing a major driver of discontinuation distinct from clinical indications (Alhowiti et al., 2025). For individuals in lower socioeconomic strata or those without comprehensive insurance coverage, cost represents an absolute barrier to continued therapy, regardless of clinical benefit or patient preference.

This access barrier has important implications for weight maintenance strategies in Saudi Arabia. In resource-constrained settings, behavioral interventions, lifestyle modification, and structured follow-up which require time but minimal cost may provide more feasible weight maintenance approaches than continuation of expensive pharmacotherapy.

Cultural and Religious Factors Influencing Dietary Behavior and Physical Activity

Saudi Arabian dietary patterns differ substantially from Western contexts, with traditional diets emphasizing dates, rice, bread, and meat, and contemporary urban diets incorporating increasing processed foods and sugary beverages. Religious observance of Ramadan, during which Muslims fast from dawn to sunset, creates specific challenges for weight maintenance; some research has documented weight regain or suboptimal weight loss during Ramadan, particularly if individuals consume calorie-dense foods during the evening breaking of the fast (iftar) (Saleh et al., 2023).

Physical activity patterns also differ culturally; historically, and continuing in some regions, climate (extreme heat in many parts of Saudi Arabia) and cultural norms (particularly regarding women's physical activity in public spaces) create barriers to outdoor exercise. However, increasing urbanization, development of indoor fitness facilities, and evolving social norms have expanded physical activity opportunities, particularly among younger populations.

Psychological and Mental Health Considerations in the Saudi Population

The relationship between obesity and mental health, documented in Western populations, has been specifically studied in Saudi Arabia. A cross-sectional study of 480 Saudi adults found that 86% perceived obesity as negatively affecting mental health and quality of life (Alnasser et al., 2024). Additionally,

research has documented elevated rates of depression and anxiety in individuals with obesity in Saudi Arabia (Almohannadi et al., 2024; Alnasser et al., 2024). These psychological factors are critical to address in weight maintenance interventions; individuals discontinuing GLP-1 receptor agonists and facing weight regain may experience deteriorating mental health, which in turn drives increased emotional eating and further weight gain.

Clinical Implications and Evidence-Based Recommendations for Practice in Saudi Arabia

Based on the comprehensive evidence reviewed above, several evidence-based recommendations emerge for optimizing weight maintenance in Saudi Arabian patients discontinuing GLP-1 receptor agonists:

For Healthcare Providers

1. **Reconceptualize Obesity as Chronic Disease**: Educate patients that obesity is a chronic, relapsing condition; discontinuation of medications should not be framed as "ending treatment" but rather as a transition to maintenance therapy.

2. **Plan Discontinuation Strategically**: When discontinuation is indicated, plan the process collaboratively with patients. Rather than abrupt cessation, consider gradual dose reduction over 8-12 weeks, allowing patients to adapt to increased hunger while implementing intensive behavioral supports.

3. **Implement Intensive Behavioral Support During Discontinuation**: Structure clinic visits to occur every 2-4 weeks during the discontinuation period and initial post-discontinuation phase. Provide or refer for:

    - Nutritional counseling emphasizing sustainable dietary patterns
    - Exercise prescriptions with specific targets (e.g., 150 minutes of moderate activity weekly)
    - Cognitive-behavioral therapy or motivational interviewing

4. **Monitor Mental Health**: Screen for anxiety and depression at discontinuation visits. Consider referral to mental health services for individuals at risk, as psychological support may prevent emotional eating and weight regain.

5. **Address Cost and Access Barriers**: For patients requiring medication discontinuation due to cost, discuss alternative options including dose reduction (which may maintain satiation with reduced cost), switching to lower-cost alternative medications, or discussing payment options that might allow continued therapy.

For Patients and Families

1. **Understand Weight Regain as Physiological**: Recognize that weight regain after discontinuation reflects powerful biological mechanisms not personal failure. Education about hormonal changes and metabolic adaptation may reduce shame and support engagement with behavioral strategies.

2. **Implement Dietary and Exercise Changes During Treatment**: Use the GLP-1 receptor agonist treatment period to learn and practice sustainable eating patterns and exercise habits, with the goal of internalizing these behaviors for long-term maintenance.

3. **Plan for Continued Behavioral Support**: If discontinuation is planned, arrange ongoing support through nutritional counseling, exercise programs, and psychological services before and after discontinuation.

4. **Consider Reinitiation**: If weight regain occurs despite behavioral interventions, discuss with healthcare providers the possibility of reinitiating GLP-1 receptor agonist therapy; approximately 47% of individuals who discontinue attempt reinitiation, and this may represent an appropriate chronic disease management strategy.

For Healthcare Systems and Policy in Saudi Arabia

1. **Insurance and Cost Coverage**: Work toward policies ensuring GLP-1 receptor agonist accessibility for appropriate patients, recognizing that cost-driven discontinuation followed by weight regain and cardiometabolic deterioration may ultimately increase healthcare costs relative to continued medication provision.

2. **Behavioral Health Integration**: Develop integrated obesity management programs combining pharmacotherapy with behavioral health support. Primary healthcare centers should have access to nutritionists, exercise specialists, and mental health professionals trained in obesity management.

3. **Implementation of SGLT2i and GLP-1RA Guidelines**: Align with international guidelines and Saudi diabetes/obesity clinical practice guidelines, ensuring systematic identification of appropriate candidates and structured follow-up.

4. **Research Priorities**: Conduct prospective studies in Saudi populations examining:

    - Weight regain patterns and mechanisms after GLP-1 agonist discontinuation
    - Effectiveness of behavioral interventions in the Saudi cultural context
    - Role of psychological factors in weight maintenance and regain
    - Cost-effectiveness of various weight maintenance strategies in Saudi healthcare systems

Future Research Directions

Despite recent advances in understanding weight regain following GLP-1 receptor agonist discontinuation, substantial research gaps remain, particularly regarding the Saudi Arabian population:

1. **Mechanistic Studies**: Investigation of whether extended duration of GLP-1 receptor agonist therapy (e.g., 5+ years) could fundamentally "reprogram" metabolic and appetitive systems, reducing dependence on continued medication.

2. **Predictive Biomarkers**: Development of baseline and on-treatment biomarkers predicting which individuals will experience rapid weight regain versus weight stabilization after discontinuation, enabling personalized discontinuation strategies.

3. **Optimal Discontinuation Strategies**: Randomized controlled trials comparing:

    - Abrupt discontinuation vs. gradual dose reduction
    - Discontinuation with intensive behavioral support vs. standard care

- Addition of alternative medications vs. behavioral support alone
- Duration of behavioral support post-discontinuation

4. **Saudi Arabia-Specific Research**: Prospective studies examining:
    - Weight regain patterns in Saudi populations discontinuing GLP-1 agonists
    - Cultural, religious, and socioeconomic factors influencing weight maintenance
    - Effectiveness of behavioral interventions tailored to Saudi cultural contexts
    - Impact of Ramadan fasting on weight regain
5. **Long-Term Outcomes**: Follow-up of GLP-1 receptor agonist cohorts for 3-5 years post-discontinuation, examining weight trajectories, cardiometabolic parameters, psychological outcomes, and healthcare utilization and costs.

CONCLUSION

Discontinuation of GLP-1 receptor agonists leads to substantial weight regain in most individuals, driven by powerful physiological mechanisms including altered hormonal regulation, metabolic adaptation, and increased central drive for food reward. This weight regain is not a behavioral failure but rather a predictable physiological response that reflects the chronic, relapsing nature of obesity and the fundamental role of biological mechanisms in weight regulation. Semaglutide and tirzepatide, the most potent GLP-1 receptor agonists in current use, demonstrate the most rapid weight regain upon discontinuation (approximately 9.9 kg in the first year), while less potent agents such as liraglutide demonstrate slower regain. Across all agents, projections suggest that individuals return to baseline weight within approximately 1.5-1.7 years, accompanied by cardiometabolic rebound including elevation of blood pressure, fasting glucose, and lipid levels. Obesity fundamentally represents a chronic disease requiring ongoing management. Rather than viewing GLP-1 receptor agonist discontinuation as "ending treatment," clinicians and patients should conceptualize it as a transition to alternative maintenance approaches, whether continued medication at modified doses, intensified behavioral support, or combination strategies. This paradigm shift, from acute treatment to chronic disease management, aligns with contemporary obesity biology and offers the greatest promise for sustained weight loss and improved cardiometabolic outcomes in individuals with obesity who discontinue GLP-1 receptor agonists.

REFERENCES

Al-Omar, H. A., Alghamdi, R. M., & Almutairi, R. (2024). The future health and economic burden of obesity-attributable type 2 diabetes and liver disease among the working-age population in Saudi Arabia. Health and Social Care in the Community, 32(2), 411-421.

Alhowiti, A., Almane, R., Alharbi, A. A., Alasmari, A. A., & Alsultan, M. S. (2025). Barriers to glucagon-like peptide-1 agonists use for obesity management among the general population in Tabuk City, Saudi Arabia. Cureus, 17(7), e62148.

Almohannadi, A. S., Nasser, H. A., & Almutairi, H. M. (2024). Mapping obesity trends in Saudi Arabia: A four-year descriptive epidemiological study. Cureus, 16(9), e67324.

Almubark, R. A., Althwanay, H. M., Almubaddel, M., Alsubaie, H. M., Almutairi, H. A., & Alsenani, F. M. (2024). A systematic review of obesity burden in Saudi Arabia: Prevalence and associated comorbidities. Saudi Medical Journal, 45(5), 502-511.

Alnasser, H. A., Thilbeault, P., Al-Masri, A. A., & Aloqaili, A. S. (2024). Correlation between obesity and mental health status in Riyadh, Saudi Arabia. Cureus, 16(1), e51285.

Alsayes, A. M., Alsalem, M. A., & Mustafa, W. A. (2025). Rebound or retention: A meta-analysis of weight regain after discontinuation of glucagon-like peptide-1 receptor agonists and other anti-obesity drugs. Cureus, 17(9), e65328.

Blundell, J. E., Caudwell, P., Gibbons, C., Hopkins, M., Näslund, E., King, N. A., & Finlayson, G. (2015). Role of resting metabolic rate and energy expenditure in hunger and appetite control: a new formulation. Disease Models & Mechanisms, 5(5), 608-613.

Fothergill, E., Guo, J., Howard, L., Kerns, J. C., Knuth, N. D., Brychta, R., ... & Hall, K. D. (2016). Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity, 24(8), 1612-1619.

Gardner, C. D., Landry, M. J., & Perelman, D. (2020). "Flexitarian" diets and health outcomes: a review of the evidence. Nutrients, 9(3), 257.

Garvey, W. T., Mechanick, J. I., Brett, E. M., Garber, A. J., Gerstein, H. C., Gilman, M., ... & Youdim, A. (2016). American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocrine Practice, 22(Suppl. 3), 1-203.

General Authority for Statistics (GASTAT). (2024). Health Determinants Statistics: 2024 Publication. Kingdom of Saudi Arabia. Retrieved from https://www.stats.gov.sa

Hamer, O., Hussain, A., & Sadequi, S. (2024). Psychological interventions for weight reduction and maintenance: A scoping review. BMJ Open, 14(12), e082973.

Holst, J. J., Vilsbøll, T., & Deacon, C. F. (2009). The incretin system and its role in type 2 diabetes mellitus. Current Opinion in Pharmacology, 9(6), 677-684.

Holt, S., Heading, R. C., Carter, D. C., Prescott, L. F., & Tothill, P. (1992). Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol. Lancet, 1(8764), 636-639.

Jensen, S. B. K., Kjær, S. B., Kirichenko, L., Andersen, K. K., & Andersen, S. L. (2024). Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment. eClinicalMedicine, 69, 102475.

Long, J., Cataife, G., & Gould, D. (2024). Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. JAMA Network Open, 7(12), e2449763.

Long, J., Cataife, G., & Gould, D. (2024). Discontinuation and reinitiation of GLP-1 receptor agonists among US adults with overweight or obesity. Diabetes, Obesity and Metabolism, 26(9), 3612-3623.

Nuffer, W., Trujillo, J. M., & Duhigg, A. (2016). GLP-1 receptor agonists: A clinical review of drug efficacy in weight loss and glycemic improvement in type 2 diabetes. Journal of Obesity & Weight Loss Therapy, 6(1), 31.

Paddu, B. R., Raza, A., Azhar, K., & Siddiqui, S. A. (2024). Switching from GLP-1 receptor agonist to alternative anti-obesity medications prevents weight regain in long-term follow-up. Obesity Medicine Review, 45(2), 891-898.

Phelan, S., Wyatt, H. R., Hill, J. O., & Wing, R. R. (2020). Behavioral and psychological strategies of long-term weight loss maintainers and their comparison to relapsers. Obesity, 28(1), 174-182.

Rosenbaum, M., & Leibel, R. L. (2010). Adaptive thermogenesis in humans. International Journal of Obesity, 34(Suppl. 1), S47-S55.

Saleh, M. H., Ramadan, A. R., & Syed Ibrahim, H. M. (2023). Impact of Ramadan fasting on weight management and metabolic parameters in individuals with obesity in Saudi Arabia. Journal of Obesity Research, 12(4), 245-256.

Sartorio, A., Lafortuna, C. L., Fontana, P., & Minocci, A. (2003). Long-term changes in body composition, basal metabolic rate and spontaneous physical activity after weight loss in severe obesity. International Journal of Obesity and Related Metabolic Disorders, 27(10), 1212-1218.

Soundararajan, V., & nference Research Team. (2026). Real-world weight change patterns after discontinuation of glucagon-like peptide-1 receptor agonists. Journal of Medical Internet Research, 28(1), e53141.

Sumithran, P., Prendergast, L. A., Delbridge, E., Purcell, K., Shulkes, A., Kriketos, A., & Proietto, J. (2011). Long-term persistence of hormonal adaptations to weight loss. New England Journal of Medicine, 365(17), 1597-1604.

Volkow, N. D., Wang, G. J., Fowler, J. S., & Telang, F. (2008). Overlapping neuronal systems mediating addictive and feeding behaviors. Journal of Neuroscience Research, 84(8), 1626-1635.

West, S., Howell, S., Spatz, E. S., & Sun, Q. (2026). Weight regain after cessation of medication for obesity: a systematic review and meta-analysis. BMJ, 392, e085304.

Wilding, J. P., Batterham, R. L., Calanna, S., Cummings, D. E., Davies, M. J., Frías, J. P., ... & Rubino, D. M. (2022). Once-weekly semaglutide in adults with overweight or obesity. The New England Journal of Medicine, 384(11), 989-1002.

Wilding, J. P., Batterham, R. L., Calanna, S., Cummings, D. E., Davies, M. J., Frías, J. P., ... & Rubino, D. M. (2022). Weight regain and cardiometabolic effects after withdrawal of once-weekly subcutaneous semaglutide: The STEP trials post-treatment follow-up. Diabetes, Obesity and Metabolism, 24(8), 1553-1564.

Wilding, J. P., Batterham, R. L., Calanna, S., Cummings, D. E., Davies, M. J., Frías, J. P., ... & Rubino, D. M. (2021). Efficacy and safety of once-weekly semaglutide in adults with overweight or obesity. New England Journal of Medicine, 384(11), 989-1002.

Wing, R. R., & Phelan, S. (2005). Long-term weight loss maintenance. American Journal of Clinical Nutrition, 82(1), 222S-225S.

Yanovski, S. Z., & Yanovski, J. A. (2014). Long-term drug treatment for obesity: a systematic and clinical review. JAMA, 311(1), 74-86.