

GLP-1 receptor agonists in adolescent obesity: Incretin-based therapies during a sensitive developmental period

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ABSTRACT

Adolescent obesity is a chronic disease associated with early cardiometabolic dysfunction and long-term health risk. Behavioral interventions alone produce modest and unsustained weight loss, leading to increasing use of pharmacotherapy. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as highly effective treatments for obesity, producing clinically significant reductions in body weight and improvements in glycemic control. Short-term safety profiles are characterized primarily by transient gastrointestinal symptoms and low rates of serious adverse events or psychiatric symptoms. However, the developmental implications and long-term effects have yet to be evaluated. The purpose of this review is to summarize existing literature concerning the use of GLP-1RAs for adolescents with obesity and to discuss the implications of GLP-1RA use in the adolescent population. This review serves to both identify areas of potential concern and to highlight the need for continued research. Although GLP-1RAs demonstrate robust efficacy for the treatment of adolescent obesity, adolescence is a sensitive period of development and critical knowledge gaps remain regarding long-term effects of GLP-1RAs on growth, pubertal development, cognition, neural reward processing, and lifelong energy balance regulation. Longitudinal and mechanistic studies are needed to determine the long-term effects on development and to guide safe, developmentally informed clinical use.

1. Introduction

Adolescent obesity is a global health issue: According to the World Health Organization, over 390 million children and adolescents aged 5–19 years around the world were overweight in 2022, including 160 million who were living with obesity (World Health Organization, n.d.). Comorbidities such as liver disease, hypertension, dyslipidemia, and diabetes start to develop in childhood, which supports the need for early treatment (Marcus et al., 2022; Shanti Vaidya & Taylor, 2025). Indeed, excess weight in childhood and adolescence detrimentally affects all aspects of immediate health, promoting insulin resistance (Klein et al., 2004; Romualdo et al., 2014; Weiss et al., 2004), chronic inflammation (Cook et al., 2000; Giannini et al., 2008), and cognitive impairment (González-Palacios et al., 2026; Meo et al., 2019), and is associated with greater risk and earlier onset of various noncommunicable diseases, such as type 2 diabetes (T2D) (Bjerregaard et al., 2018; Twig et al., 2020), cardiovascular disease (Baker et al., 2007; Sommer & Twig, 2018), and cancer (Bendor et al., 2026; Mohammadian Khonsari et al., 2023). Adolescents with obesity are also likely to have obesity in

adulthood: ~80% of adolescents with obesity will still have obesity in adulthood, and ~70% will have obesity over age 30 (Simmonds et al., 2016). Despite increased public health awareness, adolescent obesity has continued to increase, with rates of obesity for U.S. adolescents (aged 12 to 19 years old) increasing from 5% in 1960 (Ogden et al., 2002) to 22.2% in 2020 (Stierman et al., 2021).

In response to the increase in childhood obesity and its associated health concerns, the 2023 American Academy of Pediatrics' (AAP's) "Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity" emphasized the importance of pharmacotherapy in adolescents 12 years of age and older in conjunction with lifestyle change (Hampl et al., 2023). The World Health Organization (WHO), on the other hand, limits its formal clinical guidelines on GLP-1RAs for obesity to adults aged 19 and older, although these guidelines are currently under evaluation (WHO guideline on the use of glucagon-like peptide-1, 2025). The recommendation by the AAP acknowledges obesity as a chronic disease with a multifactorial and complicated etiology, and highlights the failure of behavioral interventions alone to promote long term weight loss in most individuals

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(Shanti Vaidya & Taylor, 2025). In fact, behavioral interventions, such as physical activity, nutrition, psychological counseling, technology-based solutions, or multicomponent combinations of the preceding, show only small to modest impacts on improving BMI or Health-Related Quality of Life (Davison et al., 2023; Ells et al., 2018; Henderson et al., 2025; L. Li et al., 2025; McGovern et al., 2008). For example, a 2017 meta-analysis of 44 completed randomized controlled trials and 50 ongoing studies found low quality evidence that multidisciplinary interventions involving a combination of diet, physical activity, and behavioral components reduce measures of BMI in adolescents with overweight or obesity (Al-Khudairy et al., 2017). Another meta-analysis of 34 randomized controlled trials found that pediatric obesity prevention programs caused only small changes in target behaviors with no significant reductions in BMI (Kamath et al., 2008). Furthermore, in cases where weight loss or BMI reduction are achieved with behavioral interventions, attrition rates are high and weight regain often occurs after cessation of the intervention, especially for adolescents with severe obesity (Epstein et al., 1982; Kalarchian et al., 2009; Savoye et al., 2011). Thus, the need for “early and intensive interventions” for childhood obesity (Hampl et al., 2023), in conjunction with more effective weight regulation strategies, is evident.

As clinical guidelines increasingly recognize obesity as a chronic disease requiring early intervention, efforts have also emerged to refine how obesity itself is defined and diagnosed. One such effort is the recent 2025 *Lancet Diabetes & Endocrinology* Commission, which proposed standardized diagnostic criteria for obesity to support clinical and public health decision-making (Rubino et al., 2025). While aimed towards reducing misclassification and enabling better identification of and resource allocation for obesity-related illness versus elevated health risk, these definitions may also complicate the goal of preventing and treating adolescent obesity. The committee introduced two diagnostic categories (assessed via additional measures beyond BMI such as waist circumference or body fat analysis): pre-clinical obesity for excess adiposity with increased health risk but no organ dysfunction, and clinical obesity for cases where excess adiposity is accompanied by objective signs of impaired organ function or daily activity limitations (Rubino et al., 2025). However, as noted by Fox, Cook, and Armstrong (2025), this framework inadequately accounts for the dynamic, age- and sex-specific nature of pediatric BMI and relies on measures not yet validated in youth (Fox, Cook, & Armstrong, 2025). Pediatric experts caution that labeling obesity as “preclinical” until dysfunction occurs could delay necessary intervention, leading to underestimation of disease risk by parents, deferred treatment by clinicians, and potential insurance denials, despite strong evidence that childhood obesity predicts serious future health conditions.

While debate has been spurred over the Lancet Commission's proposal for the classification of obesity, there is currently widespread interest in the use of Glucagon Like Peptide-1 Receptor Agonists (GLP-1RAs), such as liraglutide and semaglutide, for the treatment of adolescent obesity. In 2020, liraglutide was approved by the US Food and Drug Administration (FDA) for the treatment of obesity in adolescents as young as 12 years old (FDA Center for Drug Evaluation and Research, 2021), followed by the approval of semaglutide for the same indication in late 2022 (Novo Nordisk, 2022). In the years since FDA approval, the use of these drugs has rapidly increased. In 2023, around 31,000 U.S. adolescents aged 12 to 17 (representing about 0.1% of this age group) were prescribed GLP-1RAs, an increase of about 600% from 2020 (Lee et al., 2024; Miller et al., 2024). In fact, 57% of adolescents with obesity prescribed an obesity pharmacotherapy received semaglutide, underscoring rapid adoption of this drug (Kompaniyets, 2025). This dramatic shift in clinical application, as well as the many unknowns of these drugs (N. Ryan & Savulescu, 2026), highlights the urgency to critically evaluate both the efficacy and the developmental safety of GLP-1RAs in adolescent populations. Because the pharmacological properties and clinical efficacy of currently available GLP-1RAs differ substantially, a summary of their key characteristics and

adolescent clinical outcomes, discussed throughout this review, is provided in Table 1.

2. Types of GLP-1RAs: Similarities and differences

Glucagon Like Peptide-1 receptor agonists (GLP-1RAs) are a class of medications used to treat T2D and obesity. These drugs are molecularly and functionally similar to the GLP-1 incretin hormone that is naturally released from the enteroendocrine L-cells in the intestinal epithelium in response to nutrient intake, and to the GLP-1 released from the pre-proglucagon neurons in the hindbrain. In its natural form, GLP-1 regulates postprandial glucose by stimulating insulin secretion, inhibiting glucagon release, slowing gastric emptying, and increasing satiety (Zheng et al., 2024). However, endogenous GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase 4 (DPP-4), which is ubiquitously expressed on the surface of endothelial and epithelial cells. Thus, native GLP-1 has a half-life of only about 2 min and rather ephemeral biological effects (L. Hansen et al., 1999). The first GLP-1RA, exendin-4 (Ex-4), was isolated in 1992 from the saliva of the Gila monster, for which it was thought to play a role in the ability of this lizard to survive for months without eating (Eng et al., 1992). Exenatide, the synthetic pharmaceutical version of Ex-4, was shown to be beneficial for regulating blood sugar, reducing caloric intake, and lowering body weight (Bashier et al., 2014; Rosenstock et al., 2010). Although exenatide is a relatively stable molecule with a half-life of about 2 h (significantly longer than that of native GLP-1), this drug requires frequent injections for continued effect, and was therefore initially approved (in 2005) and prescribed for the treatment of T2D. However, exenatide also led the way for the development of longer-lasting GLP-1RAs. The addition of chemical moieties such as fatty acids, albumin-binding domains, or fragment crystallizable regions enhanced binding and reduced the DPP-4 degradation and renal clearance of GLP-1RAs (Bech et al., 2018). Liraglutide, a GLP-1 analog with a substitution of Arginine for Lysine and an attachment of a C-16 free-fatty acid derivative (Chia & Egan, 2009), has a half-life of approximately 13 h in humans (Min et al., 2025). Semaglutide (more commonly known by the brand names Ozempic or Wegovy, prescribed for T2D or obesity, respectively), a GLP-1 analog with a substitution of the noncoding amino acid alpha-amino isobutyric acid at position 8 and a longer fatty acid chain attached at Lysine 26 (Lau et al., 2015), has a half-life of about seven days (Min et al., 2025). With these extended dwell times, the functional actions of GLP-1RAs are significantly prolonged, thus making the drugs highly effective for influencing multiple physiological systems. Fig. 1 provides an overview of the developmental domains discussed in the following sections, along with current evidence and outstanding knowledge gaps, providing a key snapshot of this review.

3. Weight loss with adolescent GLP-1RA therapy

Clinical investigation into the use of GLP-1RAs for adolescent obesity remains limited (Katole et al., 2024; Kotecha et al., 2025), despite extensive studies in adults (Pi-Sunyer et al., 2015; Wilding, Batterham, Calanna, Davies, et al., 2021). However, emerging evidence supports their efficacy for weight reduction and metabolic improvement in this age group, similar to what is observed when prescribed during adulthood (Wong et al., 2025; Zamanian et al., 2025). In an update of a Cochrane systematic review with meta-analyses, Torbahn et al. found moderate certainty evidence that adolescent anti-obesity medications (including all drugs that have been studied in pediatric obesity populations, irrespective of their regulatory approval status) plus behavior-change interventions reduced BMI by -1.71 kg/m^2 for up to two years, compared to behavior-change intervention with or without placebo. High heterogeneity in this study was explained primarily by drug type, with semaglutide demonstrating the largest reduction in BMI (-5.88 kg/m^2) (Torbahn et al., 2024). Furthermore, a meta-analysis of seven randomized controlled trials involving 576 adolescent

Table 1
Characteristics and efficacy of GLP-1RAs studied in adolescent obesity.

Agent	Structural Modification	Half-Life	Dosing	FDA Approval for Adolescent Obesity	Key Adolescent Weight-Loss Outcomes	Additional Metabolic Outcomes	Major Limitations	Major Clinical Trials
Native GLP-1	Endogenous incretin hormone released from intestinal L-cells and hindbrain neurons	~2 min	Not clinically practical	No	Not used therapeutically due to rapid degradation by DPP-4	N/A	Extremely short half-life limits therapeutic utility	N/A
Exenatide	Synthetic form of exendin-4, originally isolated from Gila monster saliva	~2–4 h	10 µg twice daily (or 2 mg once weekly extended-release formulation)	No	BMI reductions of ~2.7–4.9%; body weight reductions of ~3–4 kg; attenuated weight regain with extended-release formulation	Improved fasting glucose tolerance, and β-cell function	Frequent injections; modest efficacy compared with newer agents	Kelly et al., 2012; Kelly et al., 2013; Fox et al., 2022; Weghuber et al., 2020
Liraglutide (Saxenda®)	GLP-1 analog with Arg→Lys substitution and C16 fatty acid side chain	~13 h	3 mg once daily	Yes (2020)	~4.6% reduction in BMI; ~4.5 kg greater weight loss than placebo; 43% achieved ≥5% BMI reduction	Improved HbA1c, fasting glucose, and blood pressure	Daily injections; substantial weight regain after discontinuation	Kelly et al., 2020; Danne et al., 2017; Klein et al., 2014; Tamborlane et al., 2019
Semaglutide (Wegovy®)	GLP-1 analog containing α-aminoisobutyric acid substitution and extended fatty acid chain	~7 days	2.4 mg once weekly	Yes (2022)	~16.1% reduction in BMI; ~15.3 kg weight loss from baseline; 73% achieved ≥5% weight loss	Improved HbA1c, fasting glucose, blood pressure, lipid profile, and liver enzymes	Weight regain after discontinuation; limited long-term developmental data	Weghuber et al., 2022

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FDA, U.S. Food and Drug Administration; HbA1c, glycated hemoglobin. Data summarized from adolescent clinical trials and studies discussed throughout this review; see Section 3 for primary weight loss references.

participants found that GLP-1RAs produced significantly greater weight loss than placebo (−4.98 kg). Subgroup analyses revealed semaglutide as the most effective type of GLP-1RA (−17.70 kg), followed by exenatide (−3.17 kg) and liraglutide (−2.26 kg) (Katole et al., 2024). Similarly, another meta-analysis of eight randomized controlled trials including 715 children and adolescents reported clinically meaningful improvements in BMI (−2.62 kg/m²), body weight (−5.54 kg), and waist circumference (−4.30 cm) with GLP-1RAs compared to placebo (Sedenho-Prado et al., 2025). These findings establish GLP-1RAs as an effective pharmacologic option for adolescent obesity, while also highlighting meaningful variability among individual agents. Because exenatide, liraglutide, and semaglutide differ substantially in their efficacy and pharmacologic characteristics, these GLP-1RAs are discussed individually below.

3.1. Weight loss with adolescent exenatide therapy

Exenatide, the first GLP-1RA to be developed, demonstrates consistent, but modest, BMI reductions in adolescents with obesity, but requires frequent administration (typically twice daily). Across two randomized trials, three months of twice daily exenatide (starting at 5 µg and titrated up to 10 µg) reduced BMI by −4.92% and −2.70%, and body weight by −3.9 kg and −3.26 kg, respectively, compared to control, although percent body fat and visceral adipose tissue were not significantly different (Kelly et al., 2012, 2013). Prolonged treatment enhanced cumulative BMI reduction, and dose-dependent effects were also observed, including transient weight rebound during down-titration (Kelly et al., 2013). Longer administration (six months) of 2.0 mg weekly exenatide encapsulated in slow release microcapsules (exenatide extended-release, ER) reduced BMI by −0.8% and body weight by −3.0 kg compared to control, as well as waist circumference by −3.2 cm and subcutaneous adipose tissue by −552 cm³ (Weghuber et al., 2020). Furthermore, in a 52-week study designed to assess weight loss maintenance, exenatide ER attenuated post-diet BMI regain in adolescents with severe obesity compared with placebo (mean increase of +4.6% for exenatide ER vs. +10.1% for placebo), suggesting that exenatide ER is also effective for preventing weight regain following weight loss (Fox et al., 2022). These studies demonstrate that exenatide produces modest but consistent improvements in adolescent BMI and weight maintenance, establishing proof-of-concept efficacy and dose-dependent durability in adolescents and paving the way for evaluation of longer-acting and more potent GLP-1RAs, such as liraglutide and semaglutide.

3.2. Weight loss with adolescent liraglutide therapy

The effects of liraglutide in adolescents with obesity are broadly consistent with those observed for exenatide. In a 56-week randomized, double-blind trial of 251 adolescents aged 12–17 years with obesity, liraglutide (starting at 0.6 mg daily and escalated to 3.0 mg daily or maximum tolerated dose) produced significantly greater reductions in BMI standard deviation score compared with placebo (estimated difference −0.22). Clinically meaningful weight loss was observed more frequently in the liraglutide group, with 43.3% and 26.1% achieving ≥5% and ≥10% BMI reductions, respectively, versus 18.7% and 8.1% in the placebo group. Absolute reductions included a −4.64% decrease in BMI and a −4.50 kg decrease in body weight compared to placebo. Notably, discontinuation of liraglutide was associated with significant weight regain; by 26 weeks post-treatment, BMI had increased approximately 4% above end-of-trial levels, approaching baseline values (Kelly et al., 2020). Shorter-duration trials of liraglutide for adolescents resulted in more modest effects. For example, in a small, exploratory study to assess safety, tolerability, and pharmacokinetics, liraglutide (escalation to 3.0 mg daily or maximum tolerated dose) resulted in small decreases in BMI z-score and body weight in both liraglutide and placebo groups (treatment difference −0.02 and −0.7 kg, respectively),

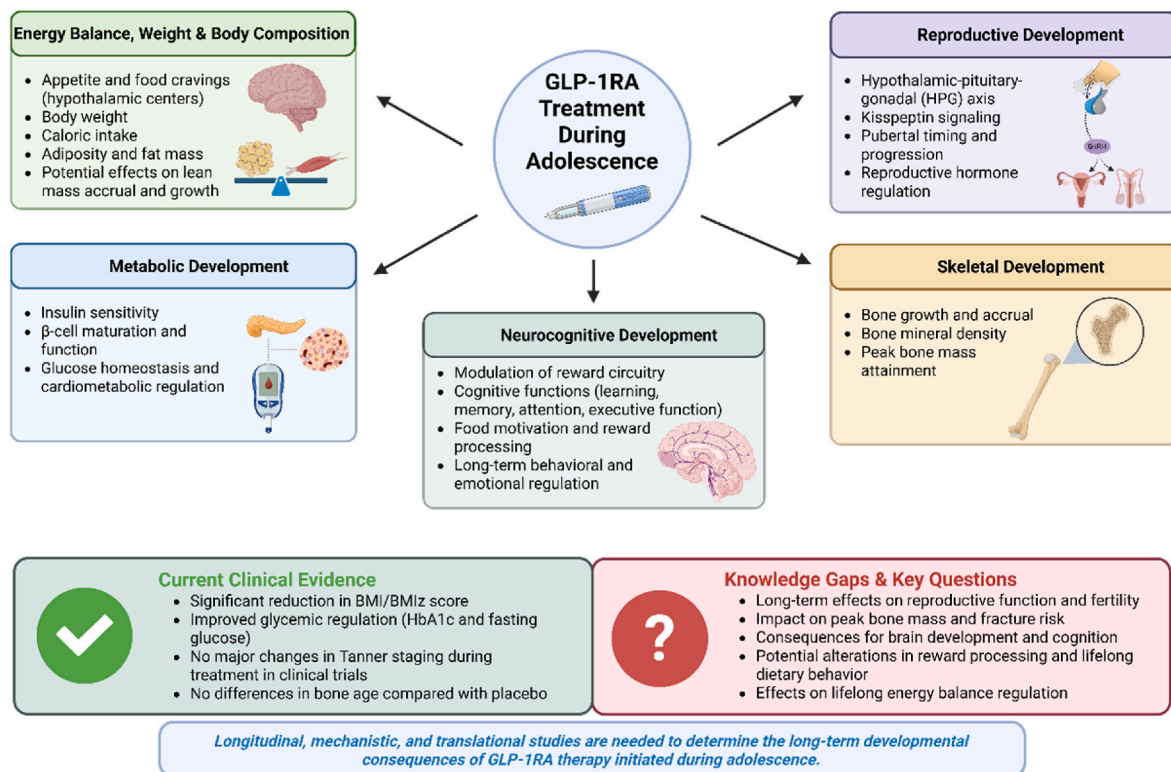


Fig. 1. Potential developmental pathways influenced by adolescent GLP-1RA exposure. Created in BioRender. Mills, A. (2026) <https://BioRender.com/n16nvb5>.

although these results were not significant, likely due to the short duration of treatment (six weeks), brief maintenance dose (maximum dose of 3.0 mg only during the last week), and small number of participants ($N = 21$) (Danne et al., 2017). Interestingly, in contrast to trials conducted in adolescents with obesity alone, weight loss effects of liraglutide in adolescents with T2D have generally been more modest (Klein et al., 2014; Tamborlane et al., 2019). In a clinical trial of liraglutide in 134 adolescents with T2D, no significant difference in BMI z-score or body weight was observed at 26 weeks despite significant HbA1c improvement (Tamborlane et al., 2019). Several factors may explain this finding, including limited full-dose exposure in this study (only ~50% reached 1.8 mg/day), background insulin therapy in some participants, and the overall anabolic action of restored insulin sensitivity (Nilsson et al., 2010). This lower magnitude of weight loss is similar to what is observed in adults with T2D prescribed liraglutide or semaglutide (Marso, Bain, et al., 2016; Marso, Daniels, et al., 2016; White et al., 2023). These data suggest that in adolescents with T2D, the primary benefit of GLP-1RA therapy may be glycemic improvement (discussed in detail in Section 5), in contrast to the more pronounced weight loss effects observed in adolescents treated for obesity alone. Overall, compared with exenatide, liraglutide produces similar reductions in BMI (approximately 4% in adolescent trials) while offering the practical advantage of once-daily rather than twice-daily administration. Semaglutide built upon this foundation of GLP-1RA use in adolescent obesity with greater potency and the need for less frequent injections.

3.3. Weight loss with adolescent semaglutide therapy

The STEP TEENS Phase 3a Trial was the basis for the FDA's approval of once-weekly semaglutide for chronic weight management in adolescents with obesity. In this double-blind, randomized, placebo-controlled trial, 201 adolescents aged 12–17 years with obesity or overweight received once-weekly subcutaneous semaglutide (2.4 mg) or placebo for

68 weeks, alongside lifestyle intervention. The semaglutide treated group had a statistically significant mean BMI reduction of -16.1% from baseline (-15.3 kg body weight), compared with a 0.6% BMI increase in the placebo group ($+2.4$ kg body weight), an estimated mean difference of -16.7% and -17.7 kg. Furthermore, a total of 73% of participants receiving semaglutide achieved at least 5% weight loss versus only 18% in the placebo group. However, within seven weeks of discontinuation of semaglutide use, participants experienced ~3% BMI rebound, suggesting the need for continued therapy for sustained weight loss (Weghuber et al., 2022). It is unknown whether this trajectory of weight regain would continue, as is observed after GLP-1RA discontinuation in adults (Wilding et al., 2022). Furthermore, the trial (as with those for exenatide and liraglutide) did not include measures of fat mass or lean mass, which may be differentially impacted during rapid weight loss associated with GLP-1RAs. To date, the STEP TEENS Phase 3a Trial remains the only trial of semaglutide involving adolescents. Despite this limited evidence base, the magnitude of weight loss observed with semaglutide substantially exceeds that reported for other GLP-1RAs. In contrast to the roughly -5% reduction in BMI observed with liraglutide and exenatide, semaglutide reduced BMI by approximately -17% from baseline, a between-trial difference of about 12%. Although cross-trial comparisons should be interpreted cautiously due to differences in study design, duration, and participant characteristics, these findings suggest that semaglutide is the most effective GLP-1RA currently evaluated for adolescent obesity.

Together, these studies suggest that GLP-1RAs, particularly semaglutide, induce clinically meaningful and sustained BMI reduction in adolescents for as long as they are on the medication. However, treatment discontinuation with all three of these GLP-1RAs results in rapid weight regain, emphasizing the necessity of long-term pharmacotherapy for weight maintenance. While exenatide and liraglutide demonstrate moderate efficacy, semaglutide resulted in the most potent effects for reducing BMI and body weight, making it a promising candidate for adolescent obesity management pending further longitudinal and

mechanistic studies. As expressed in an article by Torbahn et al. considering recent developments in anti-obesity medications, GLP-1RAs have the potential to fill the gap between the limited efficacy of health behavior and lifestyle treatment and the large effects observed with metabolic and bariatric surgery in adolescents with obesity (Torbahn et al., 2025). Nevertheless, important developmental and long-term outcome gaps remain in the current adolescent GLP-1RA literature, which are discussed in detail below.

4. Impact of adolescent GLP-1RAs on muscle mass

A primary concern of individuals taking GLP-1RAs, as well as a consideration for those not yet on these drugs, is the potential for significant loss of lean mass, including skeletal muscle, that can accompany rapid substantial weight reduction. Muscle loss can lead to reduced functional and metabolic health, weight cycling, compromised quality of life, and other adverse outcomes (Prado et al., 2018). However, it is inevitable that some loss of lean mass will accompany fat loss during weight loss interventions (McCarthy & Berg, 2021). Interestingly, according to the FDA guidelines for assessing weight management therapies (FDA, 2025), the only acceptable primary efficacy endpoints for weight loss drug trials are those related directly to changes in body weight. Body composition metrics such as muscle mass or lean mass, by contrast, are considered safety endpoints, which require far smaller cohorts for testing. This is the reason why many Phase 3 clinical trials of anti-obesity medications do not assess muscle/lean mass changes and those that do use a less accurate tool (DEXA), rather than magnetic resonance imaging (MRI), in a subset of the overall trial population (Neeland et al., 2024). This is especially true for adolescent clinical trials, for which a fewer number of studies provide even less opportunity for assessing body composition.

While the effects of GLP-1RAs on body composition have yet to be investigated in adolescents, adult studies consistently demonstrate that GLP-1RA-induced weight loss is driven primarily by reductions in total and visceral fat mass. Although modest reductions in lean mass also occur, these are proportionally smaller than fat loss, resulting in an increased relative proportion of lean mass and minimal or non-clinically meaningful effects on muscle strength and function (Neeland et al., 2024). Similar findings have been reported across multiple GLP-1RAs, including semaglutide and liraglutide, suggesting that these therapies preferentially reduce adiposity while largely preserving lean tissue (Chun et al., 2025; Lundgren et al., 2021; McCrimmon et al., 2020; Rodríguez Jiménez et al., 2024; Schmidt et al., 2025; Volpe et al., 2022; Wilding, Batterham, Calanna, Van Gaal, et al., 2021). Furthermore, the reductions in muscle size and strength observed with GLP-1RA therapy appear no greater than those associated with caloric restriction alone (Jeromson et al., 2025). Collectively, these findings suggest that GLP-1RAs in adults preferentially reduce adiposity while preserving lean mass and functional muscle during weight loss. However, whether this pattern extends to adolescent GLP-1RA therapy remains unknown.

Evidence from behavioral and surgical weight-loss interventions suggests that adolescents may similarly preserve lean mass despite substantial reductions in fat mass. Indeed, a 2013 study analyzing the composition of weight loss in adolescents with obesity using lifestyle management and sibutramine (an oral serotonin-norepinephrine reuptake inhibitor historically used as an appetite suppressant) found that weight loss was primarily from trunk fat mass, and that the percentage of lean mass increased for both boys and girls (+4.40% and +3.21%, respectively) (Parks et al., 2014). A multidisciplinary program of obesity treatment for adolescents (focused on the establishment of eating and exercise behavior changes) also showed small improvements in absolute lean mass with reduced absolute and relative body fat mass (Bianchini et al., 2014). These findings are seen not only with behavioral interventions, but with surgery as well: A meta-analysis of children and adolescents who underwent bariatric surgery reported significant reductions in fat mass (−29.3 kg), as well as smaller reductions in lean

mass (−8.5 kg) and fat-free mass (−6.5 kg) one year after surgery (Bezerra et al., 2024). Considering the similarities in weight loss trajectories with bariatric surgery and GLP-1RAs (Sabatella et al., 2025; Z. Wang et al., 2026), compositional changes in adolescents prescribed GLP-1RAs may be similar to those observed in these studies, although this remains to be directly tested.

While GLP-1RA-induced reductions in lean mass appear modest relative to losses in fat mass, a major concern associated with any decline in lean tissue is its potential impact on energy expenditure, particularly resting metabolic rate (RMR). Because skeletal muscle is a metabolically active tissue and contributes substantially to resting energy expenditure, reductions in lean mass could theoretically promote metabolic adaptation and increase susceptibility to weight regain. However, current evidence suggests that GLP-1RA therapy does not substantially reduce energy expenditure beyond what would be expected from changes in body composition. A recent scoping review concluded that GLP-1RA monotherapy and combination therapies exert minimal effects on energy expenditure, including RMR, regardless of treatment duration or magnitude of weight loss (Vieira et al., 2026). Furthermore, preclinical and clinical studies indicate that incretin-based therapies may attenuate the decline in energy expenditure typically observed during weight loss while promoting greater fat oxidation (Corbin et al., 2023; Raun et al., 2007; Ravussin et al., 2025). Although these findings are encouraging, they are derived almost exclusively from adult and animal studies. Whether GLP-1RAs similarly preserve energy expenditure and mitigate metabolic adaptation during adolescence remains unknown and warrants further investigation.

Overall, concerns regarding lean mass loss during GLP-1RA-induced weight loss are particularly important given the metabolic and functional importance of skeletal muscle. Although some loss of lean tissue inevitably accompanies weight loss, adult data consistently demonstrate that GLP-1RAs preferentially reduce fat mass while increasing the relative proportion of lean mass and preserving muscle strength. However, adolescent-specific data on GLP-1RAs and body composition remain limited. Evidence from lifestyle interventions and bariatric surgery in adolescents indicates that fat mass reductions typically occur alongside proportional smaller lean mass reductions during weight loss. Thus, these findings suggest that GLP-1RA-induced weight loss is unlikely to disproportionately compromise muscle health in adolescents, yet longitudinal studies are needed to determine precisely how these drugs influence lean mass during this sensitive developmental window.

5. Adolescent GLP-1RA therapy for glycemic control

In addition to promoting weight loss, GLP-1RAs improve glucose homeostasis, an important therapeutic target given the prevalence of insulin resistance, prediabetes, and T2D among adolescents with obesity (De Blas-Zapata et al., 2025). Clinical studies consistently demonstrate improved glycemic control following adolescent GLP-1RA treatment, with the greatest benefits observed in adolescents with established dysglycemia or T2D rather than obesity alone (Kelly et al., 2020; Klein et al., 2014; Tamborlane et al., 2019; Weghuber et al., 2022; Zhou et al., 2017). These effects are supported by the physiological role of GLP-1 in glucose regulation, and likely reflect the augmentation of a dysregulated endogenous incretin system in adolescents with obesity. Interestingly, adolescents with overweight or obesity have been shown to exhibit elevated fasting endogenous GLP-1 concentrations that correlate with markers of metabolic dysfunction, suggesting a compensatory response to insulin resistance that may become insufficient as disease progresses (Stinson et al., 2021). Consistent with this proposed mechanism, clinical trials demonstrate that GLP-1RA therapy produces meaningful improvements in glycemic control across adolescent populations, although the magnitude of benefit depends on baseline metabolic status. A meta-analysis of nine randomized clinical trials including adolescents with T2D, prediabetes, or obesity reported an overall HbA1c reduction of −0.3% compared to controls over a mean

GLP-1RA treatment duration of 18 weeks, with greater reductions in adolescents with diabetes or prediabetes (-0.72%) than with obesity alone (-0.08%). Parallel reductions were also observed for fasting plasma glucose (overall -4.0 mg/dL), again with larger effects in adolescents with T2D or prediabetes versus obesity alone (-19.4 mg/dL vs. -1.9 mg/dL, respectively). These differential responses are likely attributable to higher baseline HbA1c and fasting glucose concentrations in adolescents with dysglycemia, leading to greater absolute treatment effects (Chadda et al., 2021). A separate meta-analysis found smaller and non-significant average changes in HbA1c (-0.09%) and fasting glucose (-1.93 mg/dL) with GLP-1RA compared to placebo among children with obesity alone, highlighting the dependence of treatment magnitude on baseline metabolic impairment (Sedeno-Prado et al., 2025). Among individual GLP-1RAs, semaglutide demonstrated the most robust glycemic improvement, with an estimated treatment difference of approximately -0.3% in HbA1c (Weghuber et al., 2022), compared to -0.06% with liraglutide (Kelly et al., 2020). However, even exenatide improves glucose homeostasis: In adolescents with obesity, 24 weeks of once weekly exenatide (2 mg) lowered fasting plasma glucose by 5.2 mg/dL from baseline (Tamborlane et al., 2019), and once weekly injection of 2 mg exenatide extended release improved glucose tolerance and lowered circulating levels of proinsulin, indicating a lower demand of insulin from the periphery and less stress on the β -cells (Stenlid et al., 2023). Thus, GLP-1RAs, and semaglutide in particular, produce clinically meaningful improvements in adolescent glycemic regulation, with greater HbA1c and fasting glucose reductions in those with established dysglycemia than in those with obesity alone. Along with these effects on glucose regulation, adolescent GLP-1RA therapy may also improve broader markers of cardiometabolic health.

6. Adolescent GLP-1RA therapy for cardiometabolic health

Adolescents with obesity frequently exhibit early manifestations of cardiometabolic dysfunction, including elevated blood pressure, dyslipidemia, and hepatic steatosis, which contribute to increased cardiovascular risk later in life (De Blas-Zapata et al., 2025; Marcus et al., 2022). Although the beneficial cardiometabolic effects of GLP-1RAs have been extensively characterized in adults (see reviews by Alexiadou et al., 2024; Ferhatbegović et al., 2023; Galli et al., 2025), emerging evidence suggests that GLP-1RA therapy may also confer cardiometabolic benefits in adolescents. A meta-analysis reported that adolescent GLP-1RA treatment significantly reduced systolic blood pressure (-2.4 mmHg), but not diastolic pressure (-0.47 mmHg), compared to placebo (Sedeno-Prado et al., 2025). Similar findings were observed in a five-week trial of liraglutide (up to 3.0 mg/day), which demonstrated greater reductions in systolic (-7 mm Hg) than diastolic (-4 mm Hg) blood pressure relative to placebo (-1 and -2 mm Hg, respectively) (Danne et al., 2017). Lipid outcomes appear less responsive following GLP-1RA treatment: Across studies collectively, GLP-1RA therapy did not significantly alter total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides, despite wide individual variability (Sedeno-Prado et al., 2025). However, assessed individually, semaglutide demonstrated selective improvements in LDL and VLDL cholesterol, triglycerides, and alanine aminotransferase relative to placebo (Weghuber et al., 2022). These findings suggest that lipid improvements may be GLP-1RA-specific and proportional to the magnitude of weight loss, rather than a consistent effect of GLP-1R agonism. However, cardiometabolic effects may be modulated through a combination of weight loss-dependent and -independent mechanisms (Jacob et al., 2025). Although blood pressure generally improves with treatment, GLP-1RA therapy has also been associated with a small increase in resting heart rate ($+2.95$ beats/min) (Sedeno-Prado et al., 2025), although the clinical implications of this finding appear limited and are discussed further in the context of treatment safety in Section 10, below. Taken together, current evidence suggests that GLP-1RA therapy

confers modest but clinically meaningful improvements in cardiometabolic health among adolescents, primarily through reductions in blood pressure, with semaglutide demonstrating additional benefits for selected lipid and hepatic markers. While these findings highlight the capacity of GLP-1RAs to influence peripheral physiological systems beyond weight loss and glucose regulation, considerably less is known about their effects on the developing brain, an important consideration given the widespread distribution of GLP-1Rs throughout central nervous system circuits involved in learning, motivation, and reward.

7. Impact of adolescent GLP-1RAs on cognitive function

To date, neurocognitive outcomes have not been a focus of existing GLP-1RA clinical research; there have been no dedicated clinical trials investigating the impact of GLP-1RAs on adolescent cognitive development, a prominent gap in the literature. Since adolescence is a sensitive period for brain development and GLP-1RAs act in the brain as well as in the periphery to modulate body weight regulation, it is critical to determine whether GLP-1RAs prescribed for adolescent weight loss are impacting the development and/or functioning of the brain. Preclinical research in rodent models suggests that GLP-1RAs can modulate neural reward circuitry, part of the mechanism by which they reduce food consumption and cravings (Alhadeff et al., 2012; Anderberg et al., 2014; Kooij et al., 2024) (See also reviews of central GLP-1 reward by Badulescu et al., 2024; Skibicka, 2013). Evidence suggests these effects are not just isolated to food motivation, however, but also lower the desire for other previously rewarding activities such as drinking alcohol and drug use (Allingbjerg et al., 2023; Klausen et al., 2022; Tuesta et al., 2017). Because adolescence is characterized by extensive remodeling of metabolic, reward, and cognitive circuits (Goddings et al., 2014; Silverman et al., 2015; Spear, 2013; van Duijvenvoorde et al., 2016), including neural pathways intimately involved in food intake control (Lazzaro et al., 2025), there is a possibility that pharmacological modulation of these systems may have lasting behavioral and neural consequences. Indeed, GLP-1 receptors are expressed in brain regions involved in learning, motivation, and affect, including the hippocampus (During et al., 2003; Hsu et al., 2018; Merchenthaler et al., 1999; Netsyk et al., 2025) and the amygdala (Kinzig et al., 2002; Merchenthaler et al., 1999; Zeng et al., 2021). Although the degree to which peripheral GLP-1RAs are able to access these areas is not fully understood, clinical studies suggest that GLP-1 signaling may influence cognitive function and reward-related behaviors, including lowering activation in brain regions related to appetite and reward (Bae et al., 2020; van Bloemendaal et al., 2014, 2015). Collectively, these findings provide a strong biological rationale for investigating whether GLP-1RA therapy influences neurodevelopment during adolescence.

Despite this rationale, direct evidence evaluating developmental GLP-1RA exposure remains considerably limited. In mice, twice daily treatment with exendin-4 (0.5 mg/kg) during the pre-adolescent period (postnatal day 14–21 (Semple et al., 2013)) showed no impairment in pattern separation and memory as young adults, although behavioral measures of motor activity were moderately reduced. Furthermore, there were no changes in the *Glp1r*-expressing glutamatergic mossy cells of the dentate gyrus. However, this study did not observe changes in weight gain during exendin-4 administration, which may preclude potential cognitive effects (Cerroni et al., 2023). Weight loss itself, or a reduction in caloric intake, may contribute to improved cognition in adolescence. Preclinical models report that chronic consumption of a high fat high sugar diet during adolescence impairs learning and memory performance (Noble et al., 2019, 2021; Tsan et al., 2022) (See also reviews by Murray & Chen, 2019; Noble & Kanoski, 2016). Furthermore, cross sectional and cohort studies of adolescents with obesity show significant impairments in cognitive functions, especially attention, retention, intelligence, and cognitive flexibility (González-Palacios et al., 2026; Meo et al., 2019). Adolescent weight loss has been shown to improve not only self-representation (Barton

et al., 2004) but also selective attention, sustained attention, and short-term memory (Vanteghem et al., 2018). Weight loss through exercise interventions has further demonstrated significant improvement in executive function and attention in children and adolescents with overweight or obesity (S. Li et al., 2025), although in this case it is not possible to discern the impact of weight loss independent of the impact of exercise-induced metabolic changes. In contrast, a clinical trial of adolescents with severe obesity who underwent bariatric surgery did not demonstrate greater improvement in executive functions or memory over two years compared to a non-surgical group without weight loss (Järholm et al., 2024). Whether or not weight loss or reduced high fat high sugar diet consumption contributes to improvements in cognitive function, it remains unclear whether GLP-1RA treatment exerts direct neurocognitive effects. Potential mechanisms of benefit could include decreased inflammation and oxidative stress or improved neural signaling (Pan et al., 2024; Tan & Tan, 2019), although this has yet to be investigated. Likewise, whether adolescent GLP-1RA exposure produces persistent alterations in food-related reward processing that may influence dietary behavior in adulthood remains unknown. Overall, the available evidence suggests that weight reduction during adolescence may confer cognitive benefits in some contexts, but the lack of GLP-1RA-specific studies and the inconsistency of current findings prevent definitive conclusions regarding the neurocognitive effects of GLP-1RA therapy during adolescent development.

8. Impact of adolescent GLP-1RAs on psychiatric outcomes

Given the influence of GLP-1RAs on neural reward circuitry, particularly their depression of food and drug reward, concerns have emerged regarding their potential impact on psychiatric outcomes. Although adolescent data remain limited, the available evidence has been generally reassuring. Clinical trials have reported either improvements or no clinically meaningful changes in measures of mental health and health-related quality of life following GLP-1RA therapy. In the 68-week adolescent clinical trial of semaglutide (STEP TEENS), GLP-1RA treatment improved weight-related quality of life scores, driven primarily by improvement in physical comfort rather than psychosocial domains, suggesting measurable benefit but without clear evidence of direct psychiatric improvement (Weghuber et al., 2022). Liraglutide, on the other hand, showed no clinically relevant differences between treatment groups with respect to results on mental health questionnaires (Kelly et al., 2020). More specific evaluation of psychiatric outcomes has likewise yielded reassuring findings. A cohort study of 6912 adolescents with obesity found a 33% lower risk of suicidal ideation or attempts over three years among GLP-1RA users compared with matched behavioral-treatment controls (Kerem & Stokar, 2024). This improvement may be closely related to GLP-1RA-induced weight loss resulting in enhanced self-esteem, improvement in mood, or even better sleep (Arillotta et al., 2023), as well as positive impacts on mental health (Pierret et al., 2025) and psychosocial implications beyond the scope of this review (Krug et al., 2025). In particular, the STEP TEENS adolescent clinical trial reported no active suicidal ideation in the semaglutide group and rates of depression similar to placebo (Weghuber et al., 2022). In the principal liraglutide trial, depression prevalence was no different between placebo and liraglutide treatment. Three suicide-related events were reported across treatment and placebo groups in this study, although investigators judged these events unlikely to be treatment related, instead highlighting the vulnerability of adolescent populations independent of pharmacotherapy (Kelly et al., 2020). As a whole, current evidence does not indicate a link between GLP-1RA therapy and increased psychiatric events. In fact, GLP-1RAs may be beneficial for such indications, but limited data and heterogeneity in adult findings (Kornelius et al., 2024; Sa et al., 2026; W. Wang et al., 2024) underscore the importance of ongoing psychiatric screening and longitudinal monitoring when these drugs are prescribed during adolescence. While current evidence does not indicate major neuropsychiatric safety

concerns, the substantial alteration of energy balance resulting from GLP-1RA therapy may influence the rapid physical maturation and development of adolescence.

9. Impact of adolescent GLP-1RAs on physical development

Adolescence is a period of remarkable physical growth. Pubertal development, which occurs during this stage of life, is characterized by major somatic alterations, including sexual maturation, changes in body composition, and rapid skeletal growth (Wheeler, 1991). The growth spurt triggered by puberty increases baseline nutritional needs, requiring larger amounts of calories, protein, iron, calcium, zinc, and folate, among other macro- and micronutrients. Malnutrition during this period can delay the onset and progression of puberty, which may have implications for the proper development of organ systems and their functions later in life (Soliman et al., 2014). GLP-1RAs potentially reduce body weight and reshape body composition primarily through reductions in caloric intake (Aldawsari et al., 2023; Bettadapura et al., 2025; Flint et al., 1998). Thus, understanding the potential developmental complications of these drugs beyond weight reduction, and therefore the prudence of their use in a population whose future health is dependent upon proper growth during this sensitive stage, is critical.

9.1. Current clinical evidence for physical maturation during GLP-1RA treatment

While the current clinical trials of GLP-1RAs in adolescents are not specifically designed to assess changes in development, several of these studies use pubertal status (assessed via Tanner Stage) as a stratification factor and bone age assessment as a safety measure. Across Kelly et al.'s (2020) 56-week adolescent trial of liraglutide, there were no significant differences in Tanner Stage progressions between liraglutide and placebo for males or females (assessed via genital and breast development, respectively) (Kelly et al., 2020). In a clinical trial of 6 to 12 year old children (N = 82) with obesity prescribed once daily liraglutide or placebo, changes from baseline in pubertal status (Tanner Stage) and the proportion of female participants who had had menarche were similar in the two groups at week 56 (Fox, Barrientos-Pérez et al., 2025). The 2022 clinical trial of semaglutide in adolescents also used Tanner Stage pubertal development as a stratification factor; analyses showed no significant differences in Tanner Stage distribution between semaglutide and placebo groups for either males or females at baseline or at week 68, suggesting that semaglutide did not significantly alter pubertal progression (Weghuber et al., 2022). Limited evidence exists for impacts of GLP-1RAs on adolescent bone health: In clinical trials of adolescents with obesity taking semaglutide and liraglutide, bone age assessment, analyzed via an x-ray of the left hand and wrist, showed no differences between groups for males or females at baseline or end of study (Kelly et al., 2020; Weghuber et al., 2022). Collectively, current clinical trials have not identified significant alterations in pubertal progression or skeletal maturation during GLP-1RA treatment. However, the developmental endpoints assessed thus far are relatively limited and may not capture more subtle physiological or endocrine effects.

9.2. Potential effects on reproductive and metabolic maturation

Preclinical studies raise important mechanistic considerations that cannot be directly assessed in adolescent clinical trials. In rodent models, central administration of exenatide during the peripubertal period suppressed reproductive maturation, reducing hypothalamic kisspeptin expression and attenuating the preovulatory luteinizing hormone surge. These effects prevented vaginal opening and decreased ovarian and uterine weights, changes that were not replicated in pair-fed controls (which showed a delay in vaginal opening compared to controls), suggesting actions beyond reduced caloric intake. In contrast, central administration of endogenous GLP-1 increased luteal hormone

levels, follicular maturation, and fertility measures, highlighting complex and pathway-specific effects of GLP-1 signaling within the hypothalamic-pituitary-gonadal axis (Outeiriño-Iglesias et al., 2015). However, the degree to which peripheral GLP-1RAs are able to access central regulatory centers critical for pubertal progression remains to be determined. Taken together, while clinical trials have not demonstrated altered pubertal progression in adolescents receiving GLP-1RAs, experimental data indicate that GLP-1 pathways can directly and indirectly modulate reproductive neuroendocrine signaling during development, pointing to an urgent need for continual extensive monitoring of reproductive effects as use of these drugs expands in adolescent populations. In addition to the possibility of direct action on the reproductive pathway, the insulin sensitizing effects of GLP-1RAs may also impact pubertal development.

Adolescence is a period characterized by a natural rise in insulin resistance, a process that precedes pubertal development and is only partially accounted for by increases in adiposity (Jeffery et al., 2012). In healthy youth, this decline in insulin sensitivity, a consequence of an increase in circulating concentrations of growth hormone (GH) and insulin-like growth factor-1 (Luna et al., 1983), which oppose insulin action in peripheral tissues (Caprio et al., 2008), is accompanied by a compensatory increase in insulin secretion (Kelsey & Zeitler, 2016). While baseline insulin sensitivity and insulin secretion normally fully recover at the end of puberty, this process may be impaired in youth with obesity. In fact, as noted in a review on the subject, decreased GH action in obesity, and thus higher insulin sensitivity, may contribute to obesity-associated metabolic abnormalities (Vijayakumar et al., 2011). Given that GLP-1RAs improve insulin sensitivity, it remains unclear whether pharmacologic elevation of insulin sensitivity during the naturally insulin resistant period of adolescence could influence pubertal metabolic adaptations or alter the timing or trajectory of pubertal progression. Furthermore, puberty is associated with a transient increase in β -cell proliferation, a process that correlates with rising GH levels. Peripubertal metabolic stress blunts this proliferative response and is associated with impairments in glucose homeostasis later in life (Castell et al., 2022). GLP-1RAs strongly modulate β -cell function, demonstrating anti-apoptotic effects but also potentially resulting in β -cell exhaustion with prolonged use (Rea & Ramdass, 2025); thus, exposure during puberty may influence β -cell expansion and maturation with implications for long-term glucose homeostasis. This GLP-1RA-mediated regulation of β -cell function and insulin secretion during the adolescent period may also play a crucial role in regulating bone metabolism.

9.3. Potential effects on skeletal development

Bone health and metabolism, modulated in part by insulin action (Ravindran et al., 2025), is a critical aspect of adolescent development. Skeletal development and bone accrual exhibit rapid growth during adolescence (Weaver, 2002) and may be influenced by weight loss and altered energy balance. Approximately 40% to 60% of adult bone mass is accrued during the adolescent years (Golden et al., 2014). In fact, bone mass attained in early life is thought to be the most important modifiable determinant of lifelong skeletal health, including the prevention of osteoporosis (NIH Consensus Development Panel on Osteoporosis Prevention and Therapy, 2001). Adolescence is therefore a critical period for skeletal mineralization, necessitating diets that provide adequate nutrition and calcium for proper bone formation (Bailey et al., 2000; Prentice et al., 2006; Proia et al., 2021). Thus, the use of appetite-reducing GLP-1RAs during this period raises concerns for appropriate nutrient intake and associated skeletal development, despite preclinical evidence reporting that GLP-1RAs improve overall bone structure and strength by increasing bone formation and decreasing bone resorption, as described in an extensive systematic review (Daniilopoulou et al., 2022). The impact of GLP-1RAs on bone physiology is confounded by the varied findings observed in adult

clinical trials (Daniilopoulou et al., 2022). Whereas some studies report reductions in bone mineral density during GLP-1RA-induced weight loss, others show preservation of bone health or even reduced fracture risk, particularly among individuals with T2D (Daniilopoulou et al., 2022; M. S. Hansen et al., 2024; Jensen et al., 2024; Kong et al., 2021). These heterogeneous findings are likely due to differences in baseline metabolic status and the degree of weight loss achieved, but it is unknown whether the effects represent skeletal adaptations to reduced mechanical loading following weight reduction, direct effect of GLP-1RAs on bone, or a combination. Whether these findings extend to adolescents also remains unknown. Because skeletal development during adolescence is highly sensitive to energy balance, evidence from weight-loss interventions may provide insight into the potential consequences of GLP-1RA therapy. Although a meta-analysis of children and adolescents who underwent significant weight loss from bariatric surgery reported no impairments in bone mass (Bezerra et al., 2024), a study by Misra et al. (2020) using a control group to compare bone accrual during follow-up after surgery found that weight loss associated with sleeve gastrectomy in adolescents had negative effects on areal BMD and certain HRpQCT parameters, although bone strength estimates remained stable (Misra et al., 2020). While current adolescent GLP-1RA trials have not demonstrated overt impairment of skeletal development (as discussed in Section 9.1 (Kelly et al., 2020; Weghuber et al., 2022)), these studies were not designed to comprehensively assess bone health. Given the conflicting adult literature and the sensitivity of adolescent bone accrual to energy balance, longitudinal adolescent studies incorporating bone mineral density, bone quality, and fracture outcomes remain an important priority.

Taken together, the developmental endpoints currently reported in adolescent clinical trials may not fully capture biologically meaningful changes in development. Tanner Staging, although useful for stratifying weight loss and tracking external pubertal progression, does not directly assess hypothalamic-pituitary-gonadal axis function or reproductive hormone dynamics. Similarly, bone age derived from hand and wrist x-rays reflects the timing of skeletal maturation, but provides limited information about bone quality, microarchitecture, or peak bone mass acquisition. These measures function primarily as screening safety indicators rather than comprehensive assessments of endocrine or skeletal development. More detailed evaluations, including reproductive hormone profiles and advanced bone imaging, are necessary to determine whether prolonged GLP-1RA exposure during adolescence influences long-term development, reproductive health, or skeletal integrity. Similar gaps exist in our understanding of how GLP-1RA therapy affects skeletal muscle and lean mass accrual during this critical developmental period.

10. Overall safety of adolescent GLP-1RA therapy

Although GLP-1RAs are highly effective for adolescent weight reduction, their continuing safety in this population has yet to be fully evaluated. Short-term data from randomized trials and open-label studies indicate that GLP-1RAs are generally well tolerated in adolescents and have a safety profile broadly consistent with that in adults (Nagendra et al., 2023; Qin et al., 2024; P. M. Ryan et al., 2021; Zinman et al., 2019). Overall adverse event rates with GLP-1RAs in adolescent trials are similar to placebo, and serious adverse events (SAEs) are uncommon (Danne et al., 2017; Katole et al., 2024; Kelly et al., 2020; Tamborlane et al., 2019; Weghuber et al., 2022). Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, are the most frequent treatment-emergent adverse effects (TEAEs) and account for the largest proportion of tolerability issues, although they are usually mild and rarely necessitate treatment withdrawal. In a small six-week tolerability study of liraglutide (up to 3.0 mg/day) in 21 adolescents with obesity, every treated participant experienced at least one TEAE, but 96.5% of events were mild (e.g. abdominal pain, injection-site discomfort, mild nausea, diarrhea), with no severe TEAEs,

TEAE-related withdrawals, or deaths (Danne et al., 2017). Longer trials of liraglutide (56 weeks) and of semaglutide (68 weeks) similarly reported no severe TEAEs attributable to GLP-1RA therapy, including no acute renal failure or diabetic retinopathy (Kelly et al., 2020; Weghuber et al., 2022). A pooled analysis of seven randomized trials (N = 576 adolescents, using semaglutide, liraglutide, or exenatide) confirmed a higher odds of gastrointestinal adverse events with GLP-1RAs versus control (odds ratio 3.06; incidence comparable among all GLP-1RA agents) but found similar SAE rates between treatment and placebo arms (pooled odds ratio 1.02) (Katole et al., 2024). Hypoglycemic episodes have been reported but have not been severe in adolescent GLP-1RA trials (Danne et al., 2017; Kelly et al., 2020; Tamborlane et al., 2019; Weghuber et al., 2022). For example, there were twelve minor hypoglycemia episodes among eight liraglutide-treated participants, versus two episodes in one placebo participant in a short five week trial (Danne et al., 2017). Incidence rates of minor hypoglycemia occur more frequently with concomitant use of insulin or other sulfonylureas, necessitating closer evaluation of GLP-1RAs when used in combination with these hypoglycemic agents (Trujillo et al., 2021). Rare isolated events, such as a single moderate pancreatitis episode in a liraglutide-treated participant that resolved without intervention, have also been documented, but are infrequent and do not occur at rates statistically greater than that in placebo (Kelly et al., 2020). Overall, GLP-1RA-associated adverse events in adolescents are predominantly mild and manageable, and serious events remain uncommon, particularly when weighed against the demonstrated metabolic and cardiovascular benefits.

In addition to monitoring TEAEs, adolescent trials have evaluated physiological and laboratory safety measures to identify potential sub-clinical effects of GLP-1RA therapy. These assessments have revealed modest, reproducible physiological changes but no evidence of clinically meaningful end-organ toxicity. Small increases in resting heart rate have been observed across adolescent trials (with mean increases of anywhere from ~2 to 6 beats/min with semaglutide (Weghuber et al., 2022), liraglutide (Danne et al., 2017; Kelly et al., 2020), or exenatide (Tamborlane et al., 2019)), but without clinically significant ECG abnormalities (Danne et al., 2017). This increase in heart rate, which also occurs in adults (Lorenz et al., 2017), likely results from mediation of GLP-1 receptors in pacemaker cells of the sinus node (Lubberding et al., 2024), as well as depression of parasympathetic modulation of heart rate through inhibition of cardiac vagal neurons (Griffioen et al., 2011). However, GLP-1RA-induced increases in heart rate, regardless of their magnitude, do not appear to increase cardiovascular risk (Lorenz et al., 2017; Marso, Daniels, et al., 2016). Along with heart rate, routine hematologic, biochemical (including calcitonin), hormonal, lipid, and urinary parameters have shown no consistent, clinically important changes, and no anti-drug antibodies have been detected (Danne et al., 2017; Weghuber et al., 2022). Taken together, current data support a favorable short-term safety and tolerability profile for adolescent GLP-1RAs. However, important questions about longer-term outcomes remain and warrant continued monitoring as use expands in this population. At the same time, the demonstrated efficacy and reassuring short-term safety observed in adolescents have prompted growing interest in extending GLP-1RA therapy to younger children with obesity.

11. GLP-1RA therapy in pediatrics

Although evidence in children younger than 12 years of age remains limited, growing interest in earlier intervention has led to the evaluation of GLP-1RAs in preadolescent populations. Because obesity beginning in childhood often persists into adulthood and is associated with progressive metabolic dysfunction, effective treatment during this early developmental period has the potential to favorably alter long-term health trajectories. Clinical studies suggest that preadolescent GLP-1RAs can produce meaningful reductions in body weight and improvements in metabolic health, although the evidence base remains considerably

smaller than that for adolescents. In an 8-week trial of 24 children aged 7–11 years with obesity, daily treatment with liraglutide (starting at 0.3 mg with weekly dose escalations up to 3.0 mg or maximum tolerated dose) resulted in a significant reduction in BMI z-score from baseline to end of treatment (−0.30 vs −0.01 with placebo), with a nonsignificant decrease in absolute body weight and a modest reduction in fasting plasma glucose (Mastrandrea et al., 2019). These findings provided early proof-of-concept for GLP-1RA use in preadolescent populations. More robust evidence comes from a 56-week phase 3a trial of liraglutide (escalation up to 3.0 mg daily or maximum tolerated dose) in children aged 6 to <12 years with obesity. Liraglutide was superior to placebo with respect to percentage change in BMI (estimated difference −7.4%) and body weight (estimated difference −8.4%) from baseline (Fox, Barrientos-Pérez et al., 2025). Emerging real-world data further support the effectiveness of GLP-1RA therapy in the young population: In a multidisciplinary weight-management setting, treatment with semaglutide (1 mg weekly) in children and adolescents age 10–18 years was associated with a mean weight reduction of −9.7 kg and a BMI SDS reduction of −0.54 after 52 weeks (Boxel et al., 2024). Although observational, these findings suggest clinically meaningful benefit for children and adolescents outside of tightly controlled trial environments. Collectively, this evidence indicates that GLP-1RAs can produce meaningful BMI reductions in children under 12 years of age, with greater magnitude and durability observed with longer-term use. Given the enduring metabolic consequences of early-onset obesity, these findings suggest potential for favorably altering disease trajectory; however, as with adolescents, long-term safety, effects on growth and pubertal development, and weight stability following discontinuation remain insufficiently characterized in this preadolescent population.

12. Additional considerations for adolescent GLP-1RA therapy

Although GLP-1RAs demonstrate significant clinical efficacy for weight loss in adolescent and pediatric obesity, their use during a sensitive period of growth and development raises important concerns regarding unintended consequences. As stated by Cooper et al. in their 2023 editorial, “overuse and abuse [of GLP-1RAs] are inevitable” (Cooper et al., 2023). These concerns are echoed in a 2025 review by Bartkoski et al., who refer to pediatric GLP-1RAs and the risk of drug-drug interactions, rebound effects following discontinuation, potential for misuse, and the unknown long-term neurodevelopmental effects (Bartkoski et al., 2025). Indeed, it is not only the potential long-term effects of these drugs which must be taken into account, but unsupervised use driven by misguided self-perception of overweight or obesity, abuse by individuals with eating disorders (or overuse leading to eating disorders), use in competitive sports in which body weight is a competitive factor, and excessive or insufficient medical prescription in populations with high prevalence of obesity and poor fitness. These considerations highlight the need for careful patient selection, longitudinal monitoring, and multidisciplinary oversight when prescribing GLP-1RAs to young populations. Establishing clear clinical guidelines and education for patients, families, and providers will be essential to minimize misuse while maximizing therapeutic benefit, especially as use of these therapies continue to expand.

12.1. Future direction of adolescent GLP-1RA research

The field of incretin-based pharmacotherapy continues to evolve rapidly, with next-generation therapies demonstrating greater weight-loss efficacy and improved modes of delivery. Multi-agonist peptides targeting GLP-1 in combination with glucose-dependent insulinotropic polypeptide (GIP) and/or glucagon receptors have produced greater reductions in body weight and improvements in metabolic health than GLP-1RA monotherapy in adults (Abdrabou Abouelmagd et al., 2025; Look et al., 2025). Although these therapies have not yet been evaluated in adolescents, their enhanced potency underscores the need to carefully

assess their effects on growth, pubertal development, body composition, neurocognitive function, and long-term energy balance before widespread pediatric use. In parallel, the development of oral GLP-1RAs (e.g., Rybelsus) and other non-injectable incretin therapies (e.g., orforglipron) may improve treatment adherence, an important consideration given the relatively poor persistence with injectable therapies observed in both adults and adolescents (Gleason et al., 2024; Gomez et al., 2022; Yaron et al., 2025). While these agents have demonstrated efficacy in adults (Aroda et al., 2019; Pratley et al., 2019; Rosenstock et al., 2025, 2026; Wharton et al., 2025), their role in adolescent obesity will likewise depend on establishing long-term developmental safety alongside clinical effectiveness.

13. Conclusion

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) represent a major therapeutic advance in the management of adolescent obesity, producing clinically meaningful reductions in body weight and improvements in glycemic control with an overall favorable short-term safety profile. However, adolescence is a uniquely sensitive developmental window characterized by ongoing maturation of metabolic, endocrine, and neurobehavioral systems, raising important considerations beyond weight loss alone. The long-term effect of these pharmacotherapies on body composition changes, growth, pubertal progression, neural reward circuitry, and cognitive function remains insufficiently understood. The increasing clinical acceptance of these medications, combined with the emergence of more potent multi-agonist therapies, underscores the need for longitudinal and mechanistic research examining persistent metabolic and behavioral outcomes following adolescent exposure. Future studies should integrate developmental biology, neuroscience, and clinical outcomes to determine not only whether these drugs reduce adiposity and/or lean mass, but whether they alter lifelong energy balance regulation and adult health trajectories. Clarifying these effects will be essential to ensure that pharmacologic treatment of adolescent obesity maximizes long-term health benefits while minimizing unintended developmental consequences.

Research data

This article is a narrative review and does not report original research data. No new data were created or analyzed in the preparation of this manuscript.

Statement for studies in humans and animals

No experiments were performed for the preparation of this manuscript. Therefore, the authors state that there are no human or animal study procedures to report.

CRediT authorship contribution statement

Austin M. Mills: Conceptualization, Writing – original draft, Writing – review & editing. **Emily E. Noble:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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