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Review Article

GLP-1 receptor agonists in pediatric obesity

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed the management of obesity in adults and are now gaining attention in pediatric populations facing a dramatic rise of obesity prevalence and related comorbidities. In addition to weight loss, their role extends to cardiometabolic effects and improvements of kidney function. Liraglutide and semaglutide have demonstrated clinically meaningful efficacy in adolescents, leading to FDA and EMA approvals for patients ≥12 years. Ongoing trials are being conducted to combine GLP-1 analogues with other effective molecules or with bariatric surgery. Current evidence on safety most frequently highlights gastrointestinal adverse events, with no consistent impact on growth or pubertal development reported to date. Psychosocial dimensions, including stigma, mental health risks, and potential disordered eating, together with economic barriers and disparities in access, require careful consideration and efforts to be overcome. Implementing intensive lifestyle interventions is mandatory, including nutritional education, physical activity promotion, and family-based behavioral strategies, to support long-term weight management and address the broader determinants of health. Preliminary studies suggest complementary roles for GLP-1RAs alongside metabolic bariatric surgery in selected high-risk patients. Long-term data on safety and multidisciplinary approaches are required to define the optimal integration of pharmacotherapy into comprehensive, family-centered pediatric obesity care models.

1. Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) represent a pharmacological class initially developed for the management of type 2 diabetes mellitus (T2DM). These agents mimic the action of endogenous GLP-1, an incretin hormone secreted primarily by enteroendocrine L-cells of the distal small intestine and colon, as well as by specific neuronal populations in the brain, in response to nutrient ingestion [1]. GLP-1 slows gastric emptying and acts on hypothalamic and brainstem centers to promote satiety and reduce appetite. It also contributes to glucose and energy homeostasis by stimulating glucose-dependent insulin secretion from pancreatic β-cells while suppressing glucagon release from α-cells, thereby attenuating postprandial glycemic excursions. Beyond glycemic regulation, GLP-1 signaling has been associated with cardioprotective effects, including improvements in endothelial function, blood pressure, and lipid metabolism [2].

The discovery of GLP-1 in the early 1980s marked the start of a translational path from basic physiology to clinical innovation. Following the identification of GLP-1 receptor expression in the brain in the late 1980s and the recognition of its anorexigenic effects in rodent models in the early 1990s, the therapeutic potential of targeting this pathway became evident [3]. However, native GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), with a half-life of 1–2 min, limiting direct therapeutic use. The development of pharmacologically stable analogues, such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide, and the dual GIP/GLP-1 receptor agonist tirzepatide, overcame this barrier [4].

Two formulations have been officially approved by the U.S. Food and Drug Administration (FDA) for the management of overweight and obesity in adults: liraglutide (Saxenda®) in 2014 and semaglutide (Wegovy®) in 2021, both at higher doses than those used for diabetes treatment. Weight-reducing effects are mediated by enhanced satiety, slowed gastric emptying and decreased food

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reward via GLP-1 receptor activation in the gut and brain. In addition to weight loss and type-2 diabetes management, GLP-1 RAs treatment showed multiple benefits, including cardiometabolic improvement, ameliorated lipid profile, favorable kidney functionality, and hepatic steatosis risk reduction [1]. Moreover, recent evidence seems to support an association between GLP-1 RAs therapy of obesity and overweight adult patients and reduced overall risk of various cancer types, including lower risks of endometrial and ovarian cancer, and meningioma [5]. Their popularity has risen quickly due to ease of administration. Treatment is administered as subcutaneous injection, using a pre-filled pen device for ease of use. In particular liraglutide is administered once a day while semaglutide is administered once a week. To improve tolerability, treatment begins with a low, subtherapeutic dose, which is gradually increased: weekly for liraglutide and monthly for semaglutide [6]. Today, additional pharmacological agents are being explored as adjuncts or alternatives to GLP-1 RAs to further improve obesity management in adults [7]. Among them, cagrilintide, a dual amylin and calcitonin receptor agonist that is under investigation in combination with semaglutide; survodutide and retatrutide (dual and triple GLP-1/glucagon agonist respectively); maridebart cafraglutide that combines GLP-1 analog peptides with inhibition of the GIP receptor. In parallel, oral formulations including higher-dose semaglutide and the nonpeptide GLP-1RA orforglipron are being developed to expand therapeutic options and reduce the need for frequent injections, potentially improving adherence in younger populations [7,8].

2. Expanding interest in pediatric obesity

Children and adolescents with obesity face increased risk of cardiometabolic, respiratory, and psychosocial comorbidities that often persist in adulthood. Low self-esteem, body dissatisfaction, social isolation, anxiety, depressive symptoms, and bullying are common [9]. Long-term studies and data modeling indicate that childhood obesity strongly predicts obesity in adulthood, with relative risk estimates reaching up to three depending on age [6,10,11].

It is forecasted that between 2021 and 2050 the global prevalence of obesity in children and adolescents will increase by 120.7% [12]. By 2050, an estimated 746 million young people aged 5–24 years will have overweight or obesity, including 360 million living with obesity. This scale of disease will have substantial health, social, and economic implications, underscoring the need to identify priority populations for targeted prevention and intervention strategies [12].

In pediatric patients, obesity represents a major challenge not only for families but also for the healthcare system. The first-line treatment prescribed by pediatricians typically consists of lifestyle interventions, with intensive changes in diet and physical activity to be implemented in daily life. However, these strategies often show limited effectiveness [13], especially when poverty is faced within the family setting and means to act differently are not available [14]. Consequently, interest in the potential use of pharmacological therapies for obesity has also expanded to the pediatric population in recent years.

In early 2023, following FDA approval of semaglutide for adolescents, the American Academy of Pediatrics (AAP) issued its first updated obesity treatment guidelines in 15 years, shifting from a passive 'wait-and-see' approach to recommending intensive lifestyle interventions, anti-obesity pharmacotherapy (including GLP-1 RAs), and bariatric surgery, with clinical trials showing semaglutide achieving unprecedented BMI reductions and obesity resolution in nearly half of treated youth [15].

Accordingly, this narrative review examines key issues related to the efficacy, safety, and physical and psychological outcomes associated with GLP-1 receptor agonists in the management of paediatric obesity. A literature search was conducted across major bibliographic databases (including PubMed, Scopus, Embase, and Google Scholar). The following keywords were used: “pediatric obesity”, “children”, “adolescents”, “glucagon-like peptide-1 receptor agonists”, “GLP-1RAs”, “pharmacological therapy”, “psychological issues”, “anxiety”, “weight regain”, and “bariatric surgery.”

The search was limited to articles published in English up to September 2025 and included randomized controlled trials, observational studies, and systematic reviews and meta-analyses.

3. Current approvals and clinical evidence

Two GLP-1RAs have regulatory approval for obesity management in adolescents. In December 2020, the FDA and the Europe an Medicines Agency (EMA) for long-term weight management in adolescents 12 years of age or older with obesity, as adjunct treatments to lifestyle interventions approved liraglutide (Saxenda®) for chronic weight management in adolescents aged ≥12 years with obesity, based on a phase 3 trial (the SCALE Teens trial) on 251 pubertal adolescents (12 to <18 years of age) showing that daily liraglutide (at 3.0 mg or the maximum tolerated dose) combined with lifestyle therapy produced a mean BMI reduction of −4.6% versus placebo at 56 weeks, with 43.3% achieving ≥5% BMI reduction [16]. Similarly, in the SCALE Kids trial, a comparable study design was applied to 82 children aged 6 to <12 years, a population for whom no pharmacological treatment for obesity is currently approved. At week 56, the mean percentage change in BMI from baseline was −5.8% with liraglutide compared with +1.6% with placebo [17].

In December 2022, semaglutide (Wegovy®) was approved for adolescents aged ≥12 years with BMI ≥95th percentile, following the STEP TEENS trial, which showed a mean BMI reduction of −16.1% with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) versus +0.6% with placebo at 68 weeks, with 73% achieving ≥5% weight loss [18].

A dedicated pediatric trial of tirzepatide in participants with obesity (NCT05696847) has been completed, with results pending. Tirzepatide is a dual GIP/GLP-1 receptor agonist, the first of its kind approved, leveraging synergistic incretin effects to enhance metabolic outcomes. In adults, the SURMOUNT trial compared tirzepatide with semaglutide for obesity treatment in the US and Puerto Rico [19]. Tirzepatide achieved greater mean weight loss (−20.2% vs −13.7%) and higher proportions of participants meeting ≥10%, 15%, 20%, and 25% weight reduction targets. These results suggest a potentially more potent effect on weight loss compared with current adolescent-approved GLP-1RAs, warranting close attention to forthcoming pediatric trial outcomes [19].

A 2025 systematic review and meta-analysis analyzed 11 randomized controlled trials including 1024 pediatric patients aged 6–19 years with obesity [20]. Compared with placebo, GLP-1RAs significantly reduced body weight (mean difference [MD] −4.32 kg; 95% CI −7.02 to −1.63 kg; $p < 0.01$), BMI z-score (MD −0.28; 95% CI −0.45 to −0.10; $p < 0.01$), and waist circumference (MD −3.84 cm; 95% CI −6.97 to −0.70 cm; $p = 0.02$). A subgroup analysis of children under 12 years demonstrated a significant reduction in BMI z-score (MD −0.33; 95% CI −0.47 to −0.20; $p < 0.01$) suggesting potential efficacy in this younger population [20].

Despite these initial encouraging findings, particularly regarding improvements in BMI and body weight, pharmacological treatment of obesity in pre-adolescent children raises unique and complex considerations. During this sensitive developmental window, careful evaluation of potential long-term effects on growth trajectories, pubertal timing, bone maturation, and metabolic programming is essential, as children are undergoing active somatic and neuroendocrine development.

The psychosocial context of pre-adolescent children also differs substantially from that of adolescents. At this stage, health-related behaviors are largely shaped by parental choices, family structure, and the home food environment. Adherence to both pharmacotherapy and lifestyle modification is therefore strongly caregiver-mediated, making treatment success highly dependent on sustained family engagement. Pharmacological therapy in this population should not be considered in isolation, but rather integrated within structured, family-based behavioral interventions [21].

Furthermore, early medicalization of obesity raises concerns regarding psychological vulnerability. Pre-adolescent children are in a formative phase of identity development and self-evaluation, and exposure to chronic pharmacotherapy may influence, more profoundly than in adolescence, body image, health perception, and treatment expectations. At the same time, long-term neuropsychiatric safety data in this age group remain limited.

4. Safety and tolerability

Gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) were the most frequently reported adverse events, occurring more often than with placebo (RR 1.52; 95% CI 1.09 to 2.12; $p < 0.01$), although most events were mild to moderate in severity [20]. No consistent effects on growth or pubertal development were reported, but the follow-up duration of included RCTs was limited (typically ≤56 weeks). In the SCALE Teens trial by Kelly et al. [16], gastrointestinal adverse events were the most frequently reported, particularly nausea, vomiting, diarrhea, and constipation, occurring more often than with placebo. These events, mainly reported within the first 4–8 weeks of liraglutide dose escalation, were generally manageable with gradual dose titration. In a limited number of cases (around 10 participants), however, they led to treatment discontinuation. During the trial, three serious adverse events occurred in liraglutide-treated participants and one during follow-up, with no apparent impact on growth or development. Also in the SCALE Kids trial, in the liraglutide group, 89% of participants reported adverse events, mostly mild or moderate and self-limiting, with gastrointestinal disorders being the most common [17].

In STEP TEENS, 62% of participants on semaglutide reported at least one gastrointestinal disorder (vs 42% placebo), while liraglutide trials reported such events in up to 80% of participants. Serious adverse events were slightly more frequent with active therapy [18]. Strategies to improve tolerability include slow titration, supportive dietary measures, and avoidance of large, high-fat meals.

However, it is important to recognize that currently available pediatric safety data are derived from trials with follow-up durations typically limited to 56–68 weeks. As GLP-1RAs may be required for prolonged periods, potentially years or even decades, in children with severe obesity, the absence of long-term safety data represents a significant knowledge gap. Particular attention should be directed toward growth velocity and linear growth patterns, given the dynamic physiological changes occurring during childhood and adolescence. Although no consistent short-term effects on growth or pubertal development have been reported, longer-term surveillance is needed to exclude subtle alterations in height progression, pubertal timing, or hypothalamic–pituitary–gonadal axis maturation. Bone health also warrants careful monitoring, as rapid weight loss and potential reductions in mechanical loading may influence bone mineral accrual during critical periods of skeletal development. In addition, pancreatic safety requires ongoing evaluation, including surveillance for pancreatitis and potential alterations in exocrine function. Thyroid monitoring is advisable, particularly regarding the development of thyroid nodules, given preclinical signals observed in rodent models, even though no causal association has been established in humans. Gallbladder disease, including cholelithiasis, should also be considered, as rapid weight reduction is a recognized risk factor and has been observed in adult populations receiving GLP-1RAs.

Careful patient selection is essential. Absolute contraindications include personal or family history of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia type 2 (MEN2). Relative contraindications include prior pancreatitis, while caution is warranted in severe gastrointestinal disorders (particularly gastroparesis), pre-existing gallbladder disease, and active eating disorders.

Taken together, while short-term data support an acceptable safety profile in adolescents, the long-term risk–benefit balance remains incompletely defined. Structured, long-duration observational studies and post-marketing surveillance programs are essential to clarify the impact of chronic GLP-1RA exposure on growth, skeletal health, endocrine maturation, pancreatic and thyroid safety, and hepatobiliary outcomes in pediatric populations. A thorough medical and psychosocial assessment is recommended before initiating therapy in pediatric patients.

5. Discontinuation and weight regain

Across adult studies, weight loss achieved during GLP-1RA therapy is consistently followed by weight regain after treatment discontinuation [22]. For instance, in the STEP 3 trial participants regained approximately two-thirds of the weight lost within 6 months, reinforcing the concept that the pharmacologic benefit is largely maintained only while therapy continues [23]. In two recent systematic review and meta-analysis specifically focused on post-discontinuation outcomes [24,25]. Pooled estimates demonstrated significant weight regain during the post-treatment period, with mean differences of −5.15 kg (95% CI: −5.27 to −5.03) for semaglutide and −1.50 kg (95% CI: −2.41 to −0.26) for liraglutide [24]. Importantly, subgroup analyses identified follow-up duration as a significant modifier, with greater weight regain when post-discontinuation follow-up exceeded 26 weeks (7.31 kg vs 2.51 kg with ≤26 weeks) [25]. Consistent with these findings, cardiometabolic parameters as HbA1c, waist circumference, systolic blood pressure and fasting plasma glucose, also showed detrimental modification after discontinuation, with more pronounced worsening observed following semaglutide treatment cessation [25]. Notably, paediatric evidence is largely limited to on-treatment RCT horizons, and robust data describing long-term weight trajectory after GLP-1RA discontinuation in youth are essentially absent, leaving uncertainty as to whether the rebound magnitude mirrors adult patterns or is modified by growth, pubertal stage, and family context. This gap has direct implications for counselling and shared decision-making with families. If weight regain after cessation is substantial, GLP-1RAs may need to be conceptualized as long-term or maintenance therapies, prompting careful consideration of long-term safety, adherence, cost, and psychosocial impact in paediatric care. Future trials should therefore incorporate pre-specified discontinuation/maintenance phases and extended follow-up to quantify rebound in adiposity and cardiometabolic risk, and to identify strategies (e.g., stepped dose reduction, structured lifestyle intensification, or exercise-supported maintenance) that might attenuate regain.

6. Psychosocial and access considerations

Overweight and obesity may not only have physical health consequences but also significant mental and psychological implications, particularly in vulnerable age groups such as children and adolescents. As noted, the majority of side effects associated with GLP-1RAs are gastrointestinal; however, their drug labels also include warnings and precautions regarding potential adverse effects such as suicidal thoughts and behaviors [26]. While findings in adults concerning the impact of these medications on suicidal

ideation or attempts remain controversial, pediatric data are even more limited, though some studies have begun to explore this issue [27]. These considerations are especially important given that pediatric obesity is strongly associated with increased risks of anxiety, depression, social isolation, peer victimization, and, ultimately, suicidality [27].

The SCALE Teens trial on liraglutide reported psychiatric disorders in 13 participants (10.4%) in the treatment group and documented one suicide approximately 340 days after treatment initiation; however, the participant who died by suicide had a prior history of depression [16]. In contrast, the STEP TEENS trial on semaglutide reported a lower incidence of psychiatric adverse events in the treatment group compared to placebo (7%vs. 15%) [18].

In a retrospective cohort study of 6912 adolescents with obesity, the use of GLP-1 receptor agonists was associated with a 33% lower risk of being diagnosed with suicidal ideation or attempt compared with controls at 12 months and up to 3 years of follow-up, respectively. This effect may be explained by improvements in quality of life resulting from better obesity management, as well as preclinical evidence indicating that these agents may reduce depression-related neuropathology [27].

A relevant concern involves the psychosocial repercussions of GLP-1RA use, including peer bullying, effects on self-esteem, and the potential development of eating disorders. Body dissatisfaction is already common among adolescents, regardless of weight status [28–30], and in those with obesity, a rapid weight loss may further expose them to judgment from peers, heightening social anxiety as they are once again forced to justify their appearance. The decision to pursue pharmacological therapy rather than relying solely on diet and exercise may also be perceived by others as a personal failure, leading to stigmatizing judgments such as laziness, weakness, or lack of determination [31].

Experts in psychiatry and adolescent medicine have also expressed concern about the potential abuse of these medications and their role in triggering or worsening eating disorders, particularly avoidant/restrictive types [6,32]. By suppressing appetite and causing gastrointestinal side effects, GLP-1RAs may exacerbate voluntary food restriction, not only in terms of quantity but also variety, with possible negative consequences for nutritional status and growth.

The social and psychological effects are influenced not only by the pharmacological properties of the drug itself, but also by the economic factors related to its distribution and use.

While GLP-1RAs reduce obesity, their use in pediatric populations may also exacerbate existing health disparities. Economically and socially disadvantaged groups already face reduced access to education, health care, nutritious food, and safe spaces for physical activity, factors associated to higher rates of overweight and obesity in these populations. The high cost of these medications risks widening this gap, as access may be limited primarily to families with higher incomes [31]. Inequitable availability of these treatments and related health services could therefore worsen disparities in childhood and adolescent obesity.

In adults, evidence from the United States shows that Black and Hispanic Americans receive these medications less frequently than other groups, highlighting existing inequities [33,34]. Barriers to access and affordability remain critical challenges for treatment adherence. Moreover, healthcare disparities by race and ethnicity are driven not only by socioeconomic differences, but also by language barriers, cultural factors, and unconscious or implicit bias among providers, which can result in inadequate or inappropriate treatment offerings for certain populations. Indeed, constrained consultation times may reinforce unconscious provider selection, with clinicians often assuming that patients from racial or ethnic groups are less likely to afford, understand, or accept specific therapies [35]. Accordingly, a retrospective cohort study in pediatric populations found that anti-obesity medication prescription rates were lower among Hispanic/Latino youth and among patients from non-English-speaking families [35].

7. Bariatric surgery and glp-1ra therapy: complementary roles in adolescents

Metabolic and bariatric surgery (MBS) is a well-established, safe, and effective intervention for adolescents with severe obesity [36], typically achieving 50–60% excess weight loss within the first postoperative year and up to 75% by the second year, alongside durable improvements in cardiometabolic risk factors and psychosocial well-being [37]. Although several studies report psychological benefits following adolescent bariatric surgery, including improvements in depressive symptoms, quality of life, and self-perception [38], other evidence provides a more nuanced and less uniformly encouraging picture. Qualitative and narrative analyses suggest that a subset of adolescents may continue to experience, or even newly develop, emotional distress, body image concerns, or behavioral difficulties despite substantial weight loss [39,40]. These findings indicate that psychosocial outcomes after MBS are heterogeneous and that surgical weight reduction does not automatically resolve pre-existing psychological vulnerabilities.

Recent evidence highlights its complementary role with GLP-1RAs, either pre-operatively as a bridge to surgery and post-operatively to mitigate weight regain or suboptimal response. A recent cross-sectional analysis reported that, in the era of GLP-1RAs, MBS utilization increased among adolescents while declining in adults. This trend has been interpreted in light of the 2023 obesity management guidelines issued by the AAP, which endorsed MBS as a safe and effective treatment for severe obesity in adolescents, as well as restricted access to pharmacotherapy due to limited insurance coverage and supply shortages of GLP-1RAs, and persistent disparities in care [41].

Preliminary data of a 16-week open-label trial supports the post-sleeve gastrectomy use of liraglutide. At the end of the treatment, the 34 participants reduced BMI by 4.3% and improved fasting glucose and HbA1c in adolescents after sleeve gastrectomy, without serious adverse events. Notably, weight loss was less pronounced in those with poor initial surgical response [42].

Case reports illustrate multimodal strategies: in an 18-year-old Hispanic male with classic congenital adrenal hyperplasia and class III obesity, semaglutide achieved an 11% BMI reduction prior to surgery, together with improvements in hunger and satiety signals and emotional overeating after laparoscopic sleeve gastrectomy [43]. In a 4-year-old girl with severe obesity and type 2 diabetes, semaglutide 2 mg/week reduced HbA1c to 5.1% and lowered by 12% her percent above the 95th percentile (%BMI_{p95}), from 205% %BMI_{p95} to 190% %BMI_{p95}, demonstrating its potential role as bridging therapy prior to considering surgery [44].

In adults, the question of whether tirzepatide could approximate, though not replace, the outcomes of bariatric surgery has been raised, with future trials needed to define integrated treatment algorithms considering obesity severity, comorbidities, family preferences, and resource availability [45]. In pediatric practice, shared decision-making, nutritional monitoring, and multidisciplinary coordination remain essential.

8. Conclusions

Pharmacotherapy should never replace first-line prevention strategies, including healthy dietary habits, regular physical activity, and lifestyle counseling remain the cornerstone of management indeed. GLP-1RAs may represent a valuable adjunct in pediatric obesity care. GLP-1RA therapy in pediatric patients should be re-

served for severe, high-risk cases, within a personalized, multidisciplinary, family-centered care model, and with ongoing evaluation to ensure sustainable benefit that includes a thorough psychological assessment. Combining pharmacological therapy with structured therapeutic (eventually including MBS) and nutritional education is essential to promote adherence and to prevent both psychological and physical consequences. Long-term monitoring of their efficacy and safety is essential, especially to assess impacts on growth, pubertal development, and nutritional status. High costs and psychosocial barriers currently limit equitable access, and addressing these factors is critical.

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Declaration of competing interest

The authors state no conflicts of interest.

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