www.directivepublications.org

Journal of Diabetology Research

ISSN 2836-2446

Research Article

Childhood Obesity And Incretin Therapies With GLP-1 And GIP Receptor Agonists: Efficacy, Safety, And Prospects For Semaglutide And Tirzepatide In Children And Adolescents.

Larissa Lauretto[1]; Vitor Dácio Medeiros[1]; Vitória de Almeida Rolim Rabelo[1]; Taciane Barbosa Lopes[1]; Joana de Alencar Benevides[1]; Thalita Pinheiro Morel Alineri[1]; Gabriela Coelho de Freitas Montalvão[1]; Fernanda Maryah Leão Cunha Freitas[1]; Melissa Farias Costa de Oliveira[1]; Rebecca de Sousa Santana[1]; Sumaia Andrade Taha[1]; Camila Bassi[1]; Tâmara Gabriela da Silva[1]; Leticia Cantarino Corrêa[1]; Abigail Brito Bezerra[1]; Maiane Malaquias Martins[2]; Geizon Lee Ed Ames Ferreira de Oliveira[3]; Rodrigo Irente de Lima[4]; Glaucia da Silva Siqueira[4] ;Andrya Karla Correa Presença[5]; Délio Tiago Martins Malaquias[6]; Regina Aparecida da Conceição Cirino[6]; Regilane da S Batista[6]; Filipe JL Garcia[6]; Eliane Moreira da Silva[6]; Lucas de Souza Vieira[6]; Aline Cristina Couto da Silva[6]; Liliana M. Occulate[7]; Carlos Henrique Batista Figueiredo de Mendonça[8]; Amanda Batista Ferreira da Silva[8]; Mateus Soares Santos Araújo[9]; João Marcelo Vieira Morais[9]; Rodrigo dos Santos Oliveira Alves[9]; Vinicius Lopes Alves[10]; Thiago Augusto Rochetti Bezerra[11].

1.University of Western São Paulo (UNOESTE), Guarujá Campus, São Paulo, Brazil.
2.São Francisco College of Barreiras, Barreiras, Bahia, Brazil.
3.Paulista University (UNIP), São Paulo, Brazil
4.Mogiano Nautical Club College (FCNM), Mogi das Cruzes, São Paulo, Brazil.
5.Univag, Varzea Grande University Center, Mato Grosso, Brazil.
6.Medical Student. University of Ribeirão Preto, Guarujá Campus, São Paulo, Brazil.
7.Central University of Paraguay, School of Medicine, Pedro Juan Caballero, Paraguay
8.Federal University of Roraima (UFRR), Boa Vista, Roraima, Brazil.
9.Euro-American University Center (UNIEURO), Brasília, Federal District, Brazil
10.Unida - Universidad de la Integración de las Américas
11.Ribeirão Preto School of Medicine (FMRP/USP).

Abstract

Pediatric obesity is a chronic, multifactorial, and progressive disease associated with an early increase in cardiometabolic risk and the likelihood of persistent excess weight into adulthood. In this context, incretin-based therapies have expanded pharmacological options for children and adolescents with obesity, particularly through GLP-1 receptor agonists and combined GIP/GLP-1 agonists. The objective of this study was to analyze the current scientific evidence regarding the efficacy, safety, metabolic effects, limitations, and therapeutic prospects of liraglutide, semaglutide, and tirzepatide in the treatment of pediatric obesity. A systematic literature review was conducted, guided by the PRISMA 2020 guidelines, with searches in the PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, BVS, and SciELO databases, covering publications from 2020 through September 2026. The results demonstrated that liraglutide promotes a significant reduction in body mass index (BMI) in adolescents, while semaglutide showed a greater magnitude of response, with an average 16.1% reduction in BMI in the STEP TEENS study and improvement in cardiometabolic parameters. The most common adverse events were gastrointestinal, notably nausea, vomiting, and diarrhea, in addition to a reported case of cholelithiasis with semaglutide. Tirzepatide demonstrated a significant reduction in glycated hemoglobin and BMI in adolescents with type 2 diabetes mellitus in the SURPASS-PEDS study; however, its specific efficacy for pediatric obesity without diabetes still requires confirmation through targeted studies. It is concluded that GLP-1 agonists represent an effective alternative for selected adolescents with obesity, particularly semaglutide, while tirzepatide shows promising but still emerging results. Long-term investigations into growth, body composition, bone health, pubertal development, safety, and weight loss maintenance remain necessary.

Keywords: *Pediatric Obesity. GLP-1 Receptor Agonists. Semaglutide. Tirzepatide. Adolescents.*

***Corresponding Author:** **Thiago Augusto Rochetti Bezerra** , Ribeirão Preto School of Medicine (FMRP/USP). **Email :** rochetti.sef@gmail.com.
Received: 10-October-2026, Manuscript No. JODR - 6303 **; Editor Assigned:** 13-October-2026 **; Reviewed:** 28-October-2026, QC No. JODR - 6303 **;** **Published:** 29-October-2026, **DOI:** 10.52338/jodr.2026.6303.
Citation: **Thiago Augusto Rochetti Bezerra** , Childhood Obesity And Incretin Therapies With Glp-1 And Gip Receptor Agonists: Efficacy, Safety, And Prospects For Semaglutide And Tirzepatide In Children And Adolescents. Journal of Diabetology Research. 2026 October; 19(1). doi: 10.52338/jodr.2026.6303.
Copyright © 2026 **Thiago Augusto Rochetti Bezerra** , This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Pediatric obesity is a chronic, multifactorial, and progressive disease resulting from the interaction of genetic, neuroendocrine, metabolic, behavioral, environmental, and socioeconomic factors. Its occurrence during childhood and adolescence is particularly significant because excess body fat at this stage is associated with the early development of metabolic and cardiovascular abnormalities, in addition to increasing the likelihood of obesity persisting into adulthood. For this reason, the contemporary treatment of pediatric obesity has progressively moved beyond a model based exclusively on behavioral changes, incorporating pharmacological approaches in selected situations (WEGHUBER et al., 2022; KELLY et al., 2020).

Children and adolescents with obesity are at increased risk for insulin resistance, prediabetes, type 2 diabetes mellitus, hypertension, dyslipidemia, liver disease associated with metabolic dysfunction, obstructive sleep apnea, and musculoskeletal abnormalities. Significant psychosocial repercussions may also occur, including weight-related stigma, impaired self-esteem, and reduced quality of life, necessitating a multidisciplinary, long-term therapeutic approach (WEGHUBER et al., 2022).

Historically, lifestyle intervention—based on dietary guidance, physical activity, and behavioral modification—has been the primary therapeutic strategy for pediatric obesity. Although it remains indispensable, its effectiveness on its own may be limited in adolescents with moderate or severe obesity, especially when significant biological mechanisms regulating appetite and energy expenditure favor the maintenance of excess weight (KELLY et al., 2020; WEGHUBER et al., 2022).

Advances in our understanding of incretin physiology have significantly expanded the pharmacological options for obesity management. Glucagon-like peptide-1 (GLP-1) plays a role in regulating glucose metabolism, insulin secretion, gastric emptying, and central mechanisms related to hunger and satiety. Pharmacological stimulation of its receptors can reduce energy intake and contribute to weight loss, making GLP-1 agonists one of the leading emerging classes of treatments for obesity in adolescents (KELLY et al., 2020; WEGHUBER et al., 2022).

Liraglutide was one of the first incretin therapies to be rigorously evaluated in the adolescent population. In a randomized trial involving 251 adolescents aged 12 to under 18 years with obesity and an inadequate response to lifestyle therapy, Kelly et al. (2020) demonstrated a significantly greater reduction in the standard deviation score of body mass index with 3.0 mg of liraglutide compared to placebo. A reduction of at least 5% in BMI occurred in 43.3% of treated participants, compared with 18.7% in the placebo group, demonstrating that GLP-1 receptor modulation could provide additional clinical benefit beyond behavioral interventions (KELLY et al., 2020).

Despite its demonstrated efficacy, liraglutide also raised relevant safety concerns. Gastrointestinal adverse events occurred in 64.8% of treated adolescents, compared to 36.5% in the placebo group, and 10.4% discontinued treatment due to adverse events. These findings highlighted, from the earliest studies, the need to balance weight loss efficacy, tolerability, and careful clinical monitoring when using incretin agonists in pediatric populations (KELLY et al., 2020).

Subsequently, weekly semaglutide significantly increased the magnitude of weight loss achieved with GLP-1-based therapies. The STEP TEENS trial evaluated 201 adolescents aged 12 to under 18 years, predominantly with obesity, who were randomized to receive 2.4 mg of semaglutide weekly or placebo, both in combination with a lifestyle intervention for 68 weeks. The mean reduction in BMI was 16.1% in the semaglutide group, while the placebo group showed a mean increase of 0.6%, resulting in an estimated difference of 16.7 percentage points between the groups (WEGHUBER et al., 2022).

The results of the STEP TEENS trial were also significant when analyzing the proportion of adolescents who achieved clinically relevant weight loss. Approximately 73% of participants treated with semaglutide experienced a reduction of at least 5% in body weight, compared to only 18% in the placebo group. In addition to the reduction in BMI, improvements were observed in waist circumference, glycated hemoglobin, lipid profile, and alanine aminotransferase, suggesting that the benefits may extend beyond a simple numerical reduction in body weight (WEGHUBER et al., 2022).

However, the greater efficacy of semaglutide must be evaluated alongside its safety profile. In the STEP TEENS study, gastrointestinal adverse events occurred in 62% of treated participants, compared to 42% of those who received placebo. Gallstones were diagnosed in five participants in the semaglutide group, corresponding to approximately 4%, while no cases occurred in the placebo group, demonstrating the importance of monitoring gastrointestinal and biliary symptoms during treatment (WEGHUBER et al., 2022).

The emergence of tirzepatide has added a new dimension to incretin therapies. Unlike semaglutide, which acts predominantly as a GLP-1 receptor agonist, tirzepatide exerts simultaneous agonist activity on both GIP and GLP-1 receptors. In adults, this combination produces significant weight loss, sparking interest in its potential future application in adolescents with obesity as well (ARONNE et al., 2024; JASTREBOFF et al., 2025).

However, extrapolating the results observed in adults to children and adolescents should be done with caution. As of September 2026, the clinical evidence for tirzepatide in adolescent obesity was still expanding. The Phase 3

SURMOUNT-ADOLESCENTS study was designed to evaluate adolescents with obesity or overweight associated with comorbidities, with the primary outcome focused on the percentage change in BMI (HANNON et al., 2025).

Although definitive results from the SURMOUNT program specifically for adolescent obesity are not yet available, pediatric evidence for tirzepatide has already begun to emerge in another metabolic population. The Phase 3 SURPASS-PEDS study evaluated children and adolescents aged 10 to under 18 years with inadequately controlled type 2 diabetes mellitus and demonstrated a significant improvement in HbA1c and a reduction in BMI compared to placebo, with a safety profile generally consistent with that observed in studies conducted in adults (HANNON et al., 2025).

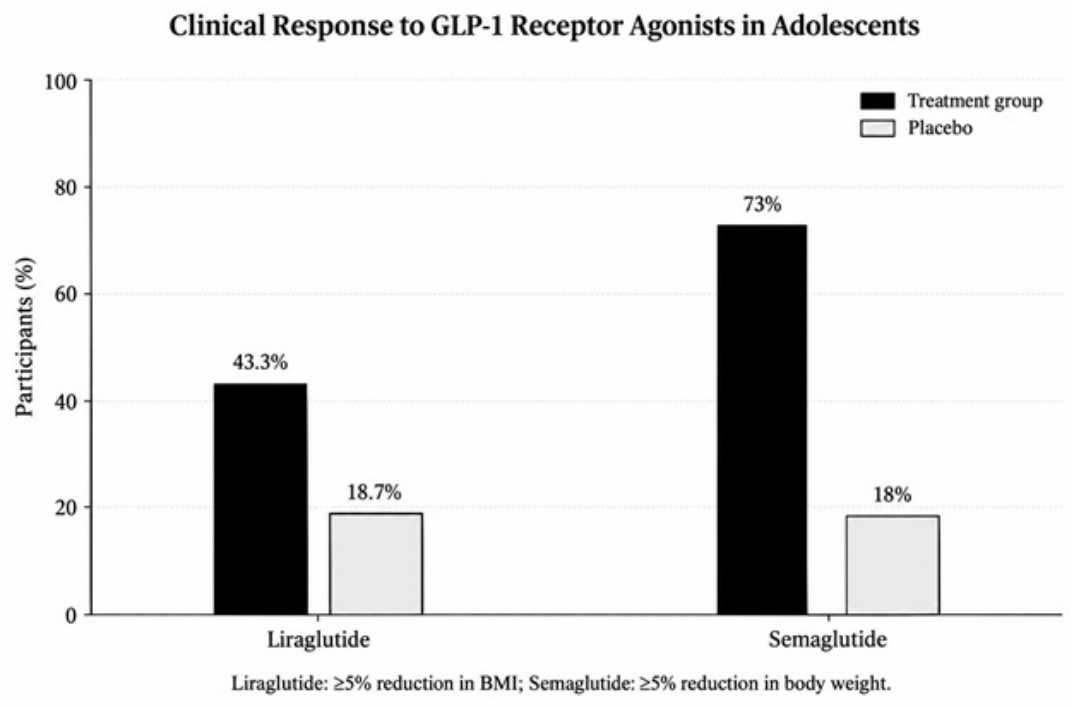
These results from SURPASS-PEDS are important because they provide initial data on pediatric exposure to tirzepatide; however, they should not be interpreted as definitive proof of efficacy for obesity in children and adolescents without diabetes. Populations with type 2 diabetes mellitus have their own metabolic characteristics, and the primary objective of the study was glycemic control. Therefore, specific results from trials dedicated to obesity are still needed before drawing conclusions about efficacy and safety in the pediatric treatment of isolated obesity (HANNON et al., 2025).

The use of incretin therapies in children and adolescents presents additional challenges compared to treatment in adults. Linear growth, pubertal development, bone maturation, body composition, nutritional intake, mental health, and psychosocial development are fundamental components of pediatric care and must be assessed alongside body weight reduction (WEGHUBER et al., 2022; KELLY et al., 2020).

Changes in body composition warrant particular attention. Pharmacologically induced weight loss does not correspond exclusively to a reduction in adipose tissue but may also involve a variable decrease in fat-free mass. In the pediatric population, this aspect takes on additional importance due to ongoing growth and muscle development, reinforcing the need for appropriate nutritional strategies and encouragement of physical activity during treatment (WEGHUBER et al., 2022).

Gastrointestinal safety is also one of the key clinical aspects of this class. Nausea, vomiting, diarrhea, and other gastrointestinal symptoms are frequently reported in trials of liraglutide and semaglutide, especially during the dose-escalation phase. Although these symptoms are generally classified as mild or moderate, they can compromise adherence, food intake, and tolerability, requiring careful monitoring in adolescents who are still growing (KELLY et al., 2020; WEGHUBER et al., 2022).

Figure 1. shows a higher proportion of clinically relevant responses in the groups receiving pharmacotherapy compared to the placebo group. In the liraglutide study, 43.3% of adolescents achieved a reduction of at least 5% in BMI, compared to 18.7% in the placebo group. In the STEP TEENS study, 73% of participants treated with semaglutide showed a reduction of at least 5% in body weight, compared with 18% in the placebo group.



Source: prepared by the authors based on Kelly et al. (2020) and Weghuber et al. (2022).

Another relevant aspect is the possible regain of weight after discontinuation of therapy. In the liraglutide trial, after discontinuation of the medication, a greater increase in BMI score was observed among previously treated participants compared to the placebo group, suggesting that part of the pharmacological benefit depends on continued treatment. This observation reinforces the need to discuss treatment duration, long-term adherence, and maintenance strategies in the pediatric population as well (KELLY et al., 2020).

The prospect of prolonged treatment during adolescence raises questions that remain largely unresolved regarding cumulative exposure, adherence, cost, the transition from pediatric to adult care, and the impact of years of therapy on growth and development. Current trials demonstrate efficacy over relatively limited periods when compared to the potential duration of a chronic disease that can persist for decades (WEGHUBER et al., 2022; KELLY et al., 2020).

It is also important to recognize that pharmacotherapy does not replace a multidisciplinary approach. Nutritional treatment, promotion of physical activity, reduction of sedentary behavior, attention to sleep, psychosocial assessment, and family involvement remain essential components of management, while medications should be incorporated as part of a broader treatment plan, especially in cases of persistent or severe obesity (WEGHUBER et al., 2022; KELLY et al., 2020).

The introduction of GLP-1 agonists—and, in the future, possibly combined GIP/GLP-1 agonist therapies—represents a paradigm shift in pediatric obesity. The magnitude of BMI reduction observed with semaglutide exceeds that found in previous studies with liraglutide, while the significant results of tirzepatide in adults and emerging data in young people with type 2 diabetes raise expectations regarding its potential future application in adolescent obesity (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

However, distinctions between proven efficacy and therapeutic expectations must remain clearly defined. Semaglutide has specific randomized evidence in adolescents with obesity, whereas pediatric evidence for tirzepatide in isolated obesity was still being consolidated as of September 2026. This distinction is essential to avoid premature extrapolation of results obtained in adults or in young people with diabetes to a growing and developing population (WEGHUBER et al., 2022; HANNON et al., 2025).

Given this scenario, an integrated analysis of the evidence regarding the efficacy, safety, and applicability of GLP-1 and GIP receptor agonists in pediatric obesity is necessary. A comparative evaluation of liraglutide, semaglutide, and tirzepatide—combined with an analysis of adverse events, metabolic effects, study limitations, and future prospects— —may help to more clearly define the role of incretin therapies in the treatment of children and adolescents with obesity (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

BACKGROUND

Pediatric obesity represents a growing public health problem due to its association with metabolic, cardiovascular, hepatic, respiratory, and psychosocial changes that can arise as early as childhood and adolescence. The persistence of obesity throughout the life course also increases the risk of cardiometabolic disease in adulthood, making it essential to develop therapeutic strategies capable of producing clinically relevant and sustained weight loss in young patients (WEGHUBER et al., 2022; KELLY et al., 2020).

Although intensive interventions targeting diet, physical activity, and behavior remain essential components of treatment, their effectiveness when used alone may be limited in adolescents with severe or persistent obesity. This limitation has led to the increasing incorporation of pharmacological therapies as part of a multimodal approach, especially when excess weight is associated with comorbidities or when there is an insufficient response to nonpharmacological measures (KELLY et al., 2020; WEGHUBER et al., 2022).

GLP-1 receptor agonists represent one of the most promising classes in this context because they simultaneously act on glycemic control, satiety, energy intake, and body weight. Clinical trials with liraglutide and, subsequently, with semaglutide have demonstrated that this class can produce greater reductions in BMI than those achieved with lifestyle intervention alone in adolescents with obesity (KELLY et al., 2020; WEGHUBER et al., 2022).

Semaglutide is particularly relevant because the STEP TEENS study demonstrated an average 16.1% reduction in BMI among adolescents treated for 68 weeks, compared with a 0.6% increase in the placebo group. In addition, 73% of participants who received semaglutide achieved a reduction of at least 5% in body weight, demonstrating a response magnitude significantly greater than that observed with previous pharmacological approaches in the adolescent population (WEGHUBER et al., 2022).

The efficacy results were accompanied by additional metabolic benefits, including a reduction in waist circumference and improvements in glycemic, lipid, and hepatic markers. These findings are relevant because pediatric obesity is often associated with insulin resistance, dyslipidemia, and metabolic liver disease, such that weight loss may have clinical impacts beyond body weight control alone (WEGHUBER et al., 2022).

On the other hand, the use of GLP-1 agonists in adolescents also raises important safety concerns. Gastrointestinal events, such as nausea, vomiting, and diarrhea, are common, and the STEP TEENS study identified cases of cholelithiasis in the semaglutide-treated group. The need to assess tolerability,

adherence, nutritional intake, and potential repercussions during growth underscores that pediatric pharmacotherapy requires careful longitudinal monitoring (WEGHUBER et al., 2022; KELLY et al., 2020).

Tirzepatide further heightens interest in incretin therapies by acting simultaneously on both GIP and GLP-1 receptors. In adults with obesity, this strategy has produced significant weight loss, which has prompted research into its application in adolescents. However, as of September 2026, specific evidence for pediatric obesity was still under development, preventing the results observed in adults from being automatically extrapolated to children and adolescents (ARONNE et al., 2024; HANNON et al., 2025).

The availability of pediatric results for tirzepatide in type 2 diabetes mellitus, as demonstrated by the SURPASS-PEDS study, represents an important advance but does not replace evidence specific to obesity. Children and adolescents with type 2 diabetes have a different metabolic profile than those with obesity without diabetes, and the study's primary outcomes were related to glycemic control (HANNON et al., 2025).

In addition to efficacy, long-term safety is one of the main reasons for further analysis of this topic. Children and adolescents are in a phase of growth, pubertal maturation, bone development, and muscle mass building; therefore, significant weight loss requires an assessment of body composition, nutritional status, and potential effects on physical and psychosocial development (WEGHUBER et al., 2022; KELLY et al., 2020).

Another relevant aspect is the potential for a reduction in fat-free mass during therapies that result in significant weight loss. Although reducing body fat is desirable, preserving lean body mass is particularly important in the pediatric population, underscoring the role of adequate protein intake, physical activity, and resistance training as complementary components of pharmacological treatment (WEGHUBER et al., 2022).

The potential need for long-term treatment must also be considered. Obesity is chronic and recurrent in nature, and studies with GLP-1 agonists suggest that some of the weight loss may be regained after discontinuation of therapy. In adolescents, this issue is even more significant, as treatment may begin many years before adulthood, raising questions about duration, adherence, cost, cumulative safety, and maintenance strategies following eventual discontinuation (KELLY et al., 2020; WEGHUBER et al., 2022).

The use of medications in children and adolescents also requires attention to psychosocial repercussions. Weight loss can improve quality of life and alleviate physical limitations, but treatment should not reinforce body stigma or make weight the sole indicator of success. Assessment of mental health, eating behavior, body image, and family context should be integrated into follow-up care, especially when long-term pharmacological therapies are used (WEGHUBER et al., 2022).

Another reason for this review is the rapid pace at which evidence in this field is evolving. While liraglutide and semaglutide have specific clinical studies in adolescents, tirzepatide is in a transitional phase between evidence from adults, pediatric data on type 2 diabetes, and studies specifically targeting adolescent obesity. This difference in the maturity of the evidence requires critical analysis (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

Thus, an updated and comprehensive review of the use of GLP-1 and GIP agonists in the treatment of childhood and adolescent obesity is warranted. An integrated analysis of the efficacy, safety, metabolic effects, adverse effects, impact on growth and body composition, and future prospects of semaglutide and tirzepatide may contribute to a more accurate understanding of the role of these therapies in contemporary pediatric practice (WEGHUBER et al., 2022; KELLY et al., 2020; HANNON et al., 2025).

OBJECTIVES

General Objective

To analyze the current scientific evidence on the use of GLP-1 and GIP receptor agonists in the treatment of obesity in children and adolescents, with an emphasis on the efficacy, safety, metabolic effects, limitations, and therapeutic prospects of semaglutide and tirzepatide (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

Specific Objectives

- To evaluate the efficacy of GLP-1 receptor agonists in reducing body weight and body mass index in adolescents with obesity, focusing primarily on the results obtained with liraglutide and semaglutide (KELLY et al., 2020; WEGHUBER et al., 2022).
- Analyze the results of the STEP TEENS study regarding the magnitude of BMI reduction, weight loss, and the proportion of participants who achieved clinically relevant responses with semaglutide (WEGHUBER et al., 2022).
- Investigate the effects of GLP-1 agonists on cardiometabolic parameters, including waist circumference, blood glucose, glycated hemoglobin, lipid profile, and liver markers in adolescents with obesity (WEGHUBER et al., 2022).
- Evaluate the major adverse events associated with the use of liraglutide and semaglutide in adolescents, with an emphasis on gastrointestinal symptoms, treatment intolerance, and biliary events (KELLY et al., 2020; WEGHUBER et al., 2022).
- Analyze the physiological mechanisms involved in the

action of GLP-1 and GIP agonists on satiety, energy intake, glycemic control, and weight loss (KELLY et al., 2020; ARONNE et al., 2024).

- Discuss the role of tirzepatide as a dual GIP/GLP-1 agonist and its potential therapeutic advantages over standalone GLP-1 receptor agonists, considering the available evidence in adults and ongoing pediatric studies (ARONNE et al., 2024; HANNON et al., 2025).
- Critically analyze the pediatric results of tirzepatide in children and adolescents with type 2 diabetes mellitus, distinguishing these findings from the specific evidence required for the treatment of pediatric obesity (HANNON et al., 2025).
- Identify the current status of studies evaluating tirzepatide in adolescents with obesity, highlighting the limitations of the evidence available through 2026 (HANNON et al., 2025).
- Assess the potential effects of pharmacological treatment on growth, pubertal maturation, bone health, and development in the pediatric population (WEGHUBER et al., 2022; KELLY et al., 2020).
- Analyze the effects of incretin therapies on body composition and discuss the importance of preserving lean body mass during significant weight loss in children and adolescents (WEGHUBER et al., 2022).
- Discuss the importance of combining pharmacotherapy, nutritional intervention, physical activity, resistance training, and behavioral support in the multidisciplinary treatment of pediatric obesity (KELLY et al., 2020; WEGHUBER et al., 2022).
- Assess the risk of weight regain after discontinuation of incretin agonists and its potential implications for the duration of treatment in adolescents (KELLY et al., 2020; WEGHUBER et al., 2022).
- Discuss aspects related to adherence, cost, tolerability, and the need for long-term treatment in the pediatric population (WEGHUBER et al., 2022).
- Analyze potential psychosocial repercussions of pharmacological treatment, including quality of life, body image, eating behavior, and weight-related stigma (WEGHUBER et al., 2022).
- Distinguish between established evidence, emerging evidence, and future perspectives regarding the use of GLP-1 and GIP receptor agonists in the management of pediatric obesity (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).
- Identify gaps in the literature and priorities for future research on efficacy, long-term safety, body composition, growth, weight maintenance, and the use of tirzepatide in children and adolescents with obesity (WEGHUBER et al., 2022; HANNON et al., 2025).

METHODOLOGY

Study Design

A systematic literature review, of a descriptive and analytical nature, was conducted, focusing on the evidence regarding the use of GLP-1 and GIP receptor agonists in the treatment of obesity in children and adolescents. The review was conducted in accordance with the PRISMA 2020 guidelines (PAGE et al., 2021).

PICO Strategy

The research question was structured according to the PICO strategy:

- **Population (P):** overweight or obese children and adolescents;
- **Intervention (I):** GLP-1 receptor agonists and combined GIP/GLP-1 agonists;
- **Comparison (C):** placebo, lifestyle intervention, other pharmacological therapies, or no pharmacotherapy;
- **Outcomes (O):** reduction in body weight and BMI, cardiometabolic changes, adverse events, body composition, growth, and development.

Databases and Search Period

The literature search was conducted in the following databases:

- PubMed/MEDLINE;
- Scopus;
- Web of Science;
- Cochrane Library;
- Virtual Health Library (BVS);
- SciELO.

Publications from January 2020 through September 2026 were prioritized.

Keywords and Search Strategy

We used Medical Subject Headings (MeSH) terms and free-text terms related to the topic, including:

"Pediatric Obesity," "Childhood Obesity," "Adolescent Obesity," "GLP-1 Receptor Agonists," "Semaglutide," "Liraglutide," "Tirzepatide," "GIP Receptor," "Body Mass Index," "Weight Loss," "Safety," "Adverse Events," "Body Composition," "Growth," and "Adolescents."

The terms were combined using the Boolean operators AND and OR, with adjustments made for each database.

The general search strategy included:

("pediatric obesity" OR "adolescent obesity" OR "childhood obesity") AND ("GLP-1 receptor agonist" OR semaglutide OR liraglutide OR tirzepatide) AND ("weight loss" OR "BMI" OR efficacy OR safety).

Inclusion Criteria

The following were included:

- randomized clinical trials;
- prospective and retrospective studies;
- observational studies;
- extension studies;
- systematic reviews;
- meta-analyses;
- studies involving children and adolescents exposed to incretin therapies;
- studies reporting results on BMI, body weight, metabolic parameters, safety, or body composition.
- Priority was given to specific studies on pediatric obesity involving liraglutide, semaglutide, and tirzepatide.

Exclusion Criteria

The following were excluded:

- isolated case reports;
- small case series;
- editorials;
- letters to the editor without original data;
- exclusively preclinical studies;
- studies conducted only in animals;
- studies lacking sufficient information on the pediatric population or the outcomes analyzed.

Studies involving only adults were excluded from the main synthesis, except when used to contextualize mechanisms of action and perspectives related to tirzepatide.

Specific Evaluation of Tirzepatide

Studies of tirzepatide were analyzed separately according to the population studied:

- adolescents with obesity;
- children and adolescents with type 2 diabetes mellitus.

This separation was made to avoid directly extrapolating results obtained in patients with diabetes to adolescents with obesity who do not have diabetes.

Study Selection

The selection process occurred in stages:

1. identification of studies in the databases;
2. removal of duplicates;
3. review of titles and abstracts;
4. application of eligibility criteria;
5. full-text review of potentially relevant studies;
6. definition of the final sample.

Data Extraction

The following information was collected:

- author and year;
- study design;
- age of participants;
- sample size;
- presence of diabetes mellitus;
- medication and dose;
- duration of treatment;
- comparison group;
- changes in weight and BMI;
- therapeutic response;
- cardiometabolic changes;
- adverse events;
- treatment discontinuation;
- body composition;
- lean body mass;
- growth and pubertal development;
- quality of life and psychosocial aspects.

Organization and Analysis of Results

The studies were organized according to the following categories:

- efficacy of liraglutide;
- efficacy of semaglutide;
- safety of GLP-1 agonists;
- cardiometabolic effects;
- body composition;
- growth and development;
- pediatric evidence on tirzepatide;
- insights from the SURMOUNT-ADOLESCENTS studies;
- multidisciplinary follow-up.

The results were evaluated through a narrative and comparative synthesis, considering effect size, safety profile, and level of evidence.

No new meta-analysis was conducted due to heterogeneity among the study populations, age groups, medications, treatment duration, and outcomes analyzed.

Assessment of Methodological Quality

Methodological quality was assessed based on the study designs, using the following as a reference:

- RoB 2, for randomized clinical trials;
- Joanna Briggs Institute (JBI) tools, for observational studies.

Risk of bias, sample size, heterogeneity, and the applicability of the results to the pediatric population were also considered.

Ethical Considerations

Since this review is based exclusively on previously published studies and publicly available data, with no direct involvement of human subjects or use of identifiable information, there was no need to submit it to the Research Ethics Committee.

RESULTS

The analysis of the evidence demonstrated a progressive expansion of the role of incretin therapies in the treatment of pediatric obesity, although the level of evidence varies substantially among the molecules evaluated. The most robust data were identified for liraglutide and, particularly, semaglutide in adolescents with obesity, while tirzepatide shows robust pediatric results in type 2 diabetes mellitus, but specific evidence for adolescent obesity is still under development as of September 2026 (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

Efficacy of liraglutide in adolescents with obesity

Kelly et al. (2020) evaluated 251 adolescents aged 12 to under 18 years with obesity and an inadequate response to lifestyle interventions. Participants were randomized to receive either 3.0 mg of liraglutide daily or a placebo, both in combination with a behavioral intervention. After 56 weeks, liraglutide demonstrated superiority in reducing the BMI standard deviation score, with an estimated difference of −0.22 compared to the placebo (KELLY et al., 2020).

Clinical response was also demonstrated by percentage reductions in BMI. A reduction of at least 5% was achieved by 43.3% of adolescents treated with liraglutide, compared with 18.7% in the placebo group, while a reduction of at least 10% occurred in 26.1% and 8.1%, resp . The estimated difference in the relative change in BMI between the groups was −4.64 percentage points (KELLY et al., 2020).

However, after discontinuation of therapy, a more pronounced increase in BMI was observed among adolescents previously treated with liraglutide. This result suggests that part of the response achieved during pharmacotherapy depends on continued treatment and reinforces the chronic nature of pediatric obesity (KELLY et al., 2020).

Table 1. Key results of liraglutide in adolescents with obesity.

Variable	Liraglutide	Placebo
Randomized participants	125	126
≥5% reduction in BMI	43.3%	18.7%
≥10% reduction in BMI	26.1%	8.1%
Gastrointestinal events	64.8%	36.5%
Discontinuation due to adverse event	10.4%	0%

Source: Authors

Subsequent meta-analyses reinforced the effect of liraglutide on pediatric BMI, although they highlighted the small number of trials, heterogeneity in metabolic outcomes, and the need for longer follow-up periods. Recent reviews confirm a significant reduction in BMI z-score with liraglutide but highlight still significant methodological limitations in the pediatric literature (KELLY et al., 2020; ROMARIZ et al., 2026).

Efficacy of semaglutide – the STEP TEENS study

Semaglutide demonstrated a substantially greater response magnitude than that observed in previous GLP-1 agonist trials. In the STEP TEENS study, 201 adolescents aged 12 to under 18 years were randomized to receive 2.4 mg of semaglutide weekly or placebo for 68 weeks, both in combination with a lifestyle intervention. The mean change in BMI was −16.1% in the semaglutide group and +0.6% in the placebo group (WEGHUBER et al., 2022).

The proportion of responders was also high. A reduction of at least 5% in body weight occurred in 73% of participants treated with semaglutide, compared to 18% of those who received placebo. The results demonstrated that weekly semaglutide can produce a weight response of a magnitude previously uncommon among pharmacological treatments for adolescent obesity (WEGHUBER et al., 2022).

In addition to weight loss, improvements were observed in waist circumference, glycated hemoglobin, triglycerides, total cholesterol, and lipoproteins (with the exception of HDL), as well as alanine aminotransferase. These results suggest that the reduction in body fat promoted by semaglutide may be accompanied by an improvement in the cardiometabolic risk profile in adolescents with obesity (WEGHUBER et al., 2022).

Table 2. Key Results of the STEP TEENS Study.

Parameter	Semaglutide 2.4 mg	Placebo
Duration	68 weeks	68 weeks
Mean change in BMI	−16.1%	+0.6%
Weight loss ≥5%	73%	18%
Gastrointestinal events	62%	42%
Gallstones	4%	0%

Source: Authors

Meta-analyses involving randomized trials have confirmed greater weight loss with GLP-1 agonists compared to placebo or lifestyle modification. In the analysis by molecule, semaglutide showed the greatest effect on weight, although the high heterogeneity and limited number of studies warrant caution in indirect comparisons between different drugs (KATOLE et al., 2024; ROMARIZ et al., 2026).

Comparison between liraglutide and semaglutide

An indirect comparison of the trials indicates a greater magnitude of weight loss with semaglutide compared to liraglutide. While Kelly et al. (2020) observed a relative difference of approximately −4.64 percentage points in BMI with liraglutide compared to placebo, the STEP TEENS trial demonstrated an average BMI reduction of 16.1% with semaglutide, highlighting a significant advance in the efficacy of pediatric incretin therapies (KELLY et al., 2020; WEGHUBER et al., 2022).

However, these values do not correspond to a direct

randomized comparison between the two molecules. The trials differed in terms of duration, study population, frequency of administration, statistical strategies, and metrics used; therefore, the apparent superiority of semaglutide should be interpreted in conjunction with meta-analyses and not as the result of a head-to-head study (KELLY et al., 2020; WEGHUBER et al., 2022; KATOLE et al., 2024).

Table 3. Comparison of Key Evidence for Liraglutide and Semaglutide.

Characteristic	Liraglutide	Semaglutide
Main study	Kelly et al. (2020)	STEP TEENS
Administration	Daily	Weekly
Primary Duration	56 weeks	68 weeks
Reduction ≥5%	43.3% of BMI	73% of body weight
Overall magnitude	Moderate	High
Predominant adverse events	Gastrointestinal	Gastrointestinal
Evidence on adolescent obesity	Consolidated	Consolidated

Source: Authors

Safety and Tolerability of GLP-1 Agonists

Gastrointestinal adverse events were the main safety finding associated with GLP-1 agonists in adolescents. In the liraglutide trial, these events occurred in 64.8% of treated participants and in 36.5% of controls, while in the STEP TEENS trial they occurred in 62% and 42%, respectively. Nausea, vomiting, and diarrhea were the most common and occurred more frequently during dose escalation (KELLY et al., 2020; WEGHUBER et al., 2022).

Semaglutide also showed a significant incidence of biliary events, with cholelithiasis in five participants—corresponding to approximately 4% of the treated group—compared with no cases in the placebo group. Although the absolute number was small, this finding reinforces the need for clinical evaluation in the presence of abdominal pain and other symptoms consistent with gallbladder disease during rapid weight loss (WEGHUBER et al., 2022).

Recent meta-analyses confirm a significant increase in gastrointestinal events among adolescents treated with GLP-1 agonists, without a corresponding increase in serious adverse events, suggesting an overall acceptable safety profile during the evaluated periods, although long-term data remain limited (KATOLE et al., 2024; ROMARIZ et al., 2026).

Table 4. Key Safety Aspects of GLP-1 Agonists.

Event/Issue	Evidence
Nausea	Common
Vomiting	More frequent than with placebo
Diarrhea	Frequent
General gastrointestinal events	Main limitation regarding tolerability
Gallstones	Sign observed with semaglutide
Discontinuation	Higher in some treatment groups
Serious events	No consistent increase demonstrated
Long-term safety	Still insufficiently established

Source: Authors

Cardiometabolic effects

The metabolic effects of GLP-1 agonists were not limited to body weight. In the STEP TEENS study, more favorable reductions were observed in waist circumference, HbA1c, triglycerides, total cholesterol, certain lipid fractions, and alanine aminotransferase in the semaglutide group, suggesting a potential benefit regarding changes associated with insulin resistance and visceral adiposity (WEGHUBER et al., 2022).

A 2025 meta-analysis on metabolic outcomes and safety of GLP-1 agonists in pediatric obesity confirmed anthropometric benefits and identified favorable effects on various metabolic markers, although the magnitude varied across studies. The authors emphasized that the number of trials is still limited and that the effects on long-term cardiometabolic outcomes remain less well established than the efficacy on weight (SEDENHO-PRADO et al., 2025).

Tirzepatide in Children and Adolescents with Type 2 Diabetes – SURPASS-PEDS

The SURPASS-PEDS study provided the first robust Phase 3 evidence on tirzepatide in a pediatric population. A total of 99 participants aged 10 to under 18 years with type 2 diabetes mellitus inadequately controlled with metformin and/or basal insulin were randomized to receive tirzepatide 5 mg, tirzepatide 10 mg, or placebo. The primary outcome was the change in HbA1c after 30 weeks (HANNON et al., 2025).

Tirzepatide resulted in a mean reduction in HbA1c of 2.23 percentage points in the pooled analysis, while placebo resulted in an increase of 0.05 percentage points, resulting in a treatment difference of −2.28 percentage points. The glycemic benefit persisted throughout the 52-week follow-up period, demonstrating substantial efficacy in type 2 diabetes with onset in youth (HANNON et al., 2025).

The effects on BMI were also significant. At week 30, reductions of 7.4% were observed with tirzepatide 5 mg and 11.2% with 10 mg, while the placebo group showed a reduction of only 0.4%. These data provide strong evidence of tirzepatide's effect on body weight in young people, although in a population selected for type 2 diabetes and not specifically for obesity alone (HANNON et al., 2025).

The most common adverse events in the SURPASS-PEDS trial were gastrointestinal, predominantly mild to moderate in severity, and their frequency decreased over the course of

the treatment . Two participants in the 5 mg group discontinued therapy due to adverse events; no deaths were reported, and the safety profile was considered consistent with that previously observed in adults (HANNON et al., 2025).

Table 5. Key Results of SURPASS-PEDS.

Parameter	Tirzepatide	Placebo
Total participants	65 (5 mg + 10 mg)	34
Age	10 to <18 years	10 to <18 years
Population	Juvenile DM2	Juvenile DM2
Change in HbA1c – Week 30	−2.23% (pooled)	+0.05%
BMI Change – 5 mg	−7.4%	—
Change in BMI – 10 mg	−11.2%	—
Change in BMI – placebo	—	−0.4%
Most common events	Gastrointestinal	Less frequent

Source: Authors

Tirzepatide for Adolescent Obesity—State of the Evidence

Despite the promising results of the SURPASS-PEDS trial, as of September 30, 2026, no definitive results had been published from the Phase 3 SURMOUNT-ADOLESCENTS trial, which specifically targeted the treatment of obesity or overweight with comorbidities in adolescents. Therefore, the efficacy of tirzepatide specifically in the treatment of adolescent obesity should remain classified as emerging evidence until these studies are completed and published (HANNON et al., 2025).

This distinction is crucial because the pediatric evidence for tirzepatide available to date derives from a population with type 2 diabetes mellitus. Therefore, it was not yet possible to consider tirzepatide equivalent to semaglutide in terms of specific evidence for adolescent obesity (WEGHUBER et al., 2022; HANNON et al., 2025).

Table 6. Status of pediatric evidence for tirzepatide.

Program	Population	Status as of September 30, 2026	Interpretation
SURPASS-PEDS	Ages 10–<18 with Type 2 Diabetes	Published	Demonstrated glycemic efficacy and reduction in BMI
SURMOUNT-ADOLESCENTS	Adolescents with obesity/ overweight and comorbidities	Ongoing	No definitive published evidence for obesity yet
SURMOUNT-ADOLESCENTS-2	Adolescents with obesity and comorbidities	Ongoing	Future results needed

Source: Authors

Body Composition, Growth, and Development

Large pediatric trials have demonstrated significant reductions in weight and BMI, but have provided less extensive information on detailed body composition, bone mineral density, and the consequences of exposure during several years of growth. This gap is particularly relevant during adolescence, a period characterized by rapid acquisition of bone and muscle mass, pubertal maturation, and important physiological changes in body composition (KELLY et al., 2020; WEGHUBER et al., 2022).

The currently available results do not show a consistent indication of impaired linear growth during the periods studied; however, the follow-up period is short relative to the potential duration of treatment for a disease that may persist into adulthood. Therefore, height, growth velocity, pubertal development, nutritional intake, and body composition should remain among the primary safety outcomes in future long-term pediatric studies (KELLY et al., 2020; WEGHUBER et al., 2022).

Summary of Key Findings

The synthesis of the evidence demonstrated clear progress in the efficacy of pediatric incretin therapies. Liraglutide promotes a moderate reduction in BMI and has well-established randomized evidence, while semaglutide showed the greatest magnitude of weight loss currently demonstrated in a specific trial of adolescents with obesity. Meta-analyses confirm that GLP-1 agonists are superior to placebo or lifestyle intervention alone for weight loss in adolescents (KELLY et al., 2020; WEGHUBER et al., 2022; KATOLE et al., 2024).

The main tolerability limitation was gastrointestinal events, particularly nausea, vomiting, and diarrhea. The trials did not demonstrate a consistent increase in serious events during the evaluated periods, but issues related to cholelithiasis, nutritional

status, lean body mass, pubertal development, and long-term exposure remain relevant to pediatric safety (KELLY et al., 2020; WEGHUBER et al., 2022; SEDENHO-PRADO et al., 2025).
Tirzepatide represents the main future prospect. The SURPASS-PEDS trial has already demonstrated a significant reduction in HbA1c and BMI in adolescents with type 2 diabetes, providing important initial evidence regarding pediatric efficacy and safety. However, these results cannot be considered equivalent to demonstrating specific efficacy for obesity without diabetes, which depends on studies dedicated to adolescent obesity (HANNON et al., 2025).

DISCUSSION

The results of this review demonstrate that incretin therapies represent a significant shift in the treatment of pediatric obesity, particularly among adolescents with moderate or severe obesity who have shown an insufficient response to traditional interventions. Studies with liraglutide and semaglutide show that GLP-1 receptor agonists can significantly enhance weight loss when combined with lifestyle interventions, while tirzepatide emerges as a promising alternative due to its dual mechanism of action on GIP and GLP-1 receptors (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).
Kelly et al. (2020) laid one of the key foundations for the use of incretin pharmacotherapy in adolescents by demonstrating the superiority of liraglutide over placebo. The higher proportion of participants who achieved a reduction of at least 5% and 10% in BMI demonstrated that pharmacological activation of the GLP-1 receptor can provide an additional benefit to behavioral interventions in patients with persistent obesity (KELLY et al., 2020).
Despite this advance, the magnitude of the effect observed with liraglutide was relatively modest when compared with semaglutide in the STEP TEENS trial. Weghuber et al. (2022) demonstrated an average 16.1% reduction in BMI with semaglutide, while the placebo group showed a 0.6% increase. The contrast between these results suggests a significant improvement in efficacy within the GLP-1 agonist class itself, although the trials were not designed for a direct comparison between the molecules (KELLY et al., 2020; WEGHUBER et al., 2022).
The comparison between liraglutide and semaglutide, however, should be interpreted with caution. Kelly et al. (2020) and Weghuber et al. (2022) employed study designs, durations, efficacy metrics , and study populations that are not entirely equivalent. Therefore, the results do not constitute a direct comparison between the two drugs. Nevertheless, subsequent systematic reviews and meta-analyses indicate that semaglutide is the GLP-1 agonist with the greatest effect on body weight among the medications studied in adolescents (KATOLE et al., 2024; ROMARIZ et al., 2026).
The high efficacy of semaglutide is clinically significant because adolescents with severe obesity often show a limited response to behavioral interventions alone. In the STEP TEENS trial, 73% of treated participants achieved a weight loss of at least 5% of their body weight, compared to 18% in the placebo group. The benefit, however, was not limited to weight, as improvements were also observed in waist circumference, HbA1c, lipids, and ALT, suggesting potentially favorable effects on cardiometabolic risk (WEGHUBER et al., 2022). Despite these findings, metabolic outcomes are not entirely consistent across different studies. Sedenho-Prado et al. (2025), in a meta-analysis of pediatric studies, observed significant reductions in weight, BMI, and abdominal circumference, but did not identify consistent changes in all metabolic markers. This divergence suggests that cardiometabolic effects may depend on the population, treatment duration, and degree of baseline metabolic abnormalities (SEDENHO-PRADO et al., 2025).
Another important aspect is that the greater magnitude of weight loss must be analyzed in conjunction with safety. Both Kelly et al. (2020) and Weghuber et al. (2022) identified gastrointestinal events as the most frequent adverse reactions, with rates higher than those observed in the placebo groups. Nausea, vomiting, and diarrhea were particularly common during dose-escalation periods, which may influence adherence and tolerability in a pediatric population (KELLY et al., 2020; WEGHUBER et al., 2022).
The most recent meta-analyses confirm this profile. Katole et al. (2024) and Romariz et al. (2026) identified an increased risk of gastrointestinal symptoms in the pediatric population treated with GLP-1 agonists. Despite this, the available studies have not demonstrated a consistent increase in serious adverse events, suggesting that the main short-term limitation is related more to tolerability than to frequent serious complications (KATOLE et al., 2024; ROMARIZ et al., 2026).
The finding of cholelithiasis in the STEP TEENS study warrants specific attention. Five participants treated with semaglutide developed gallstones, while no cases were observed in the placebo- . This safety signal should be interpreted with the understanding that rapid weight loss itself may increase the risk of biliary disease, making it difficult to completely distinguish between the direct effect of the drug and the effect associated with weight loss (WEGHUBER et al., 2022).
The duration of treatment represents another issue that has not yet been fully resolved. In the trial by Kelly et al. (2020), following discontinuation of liraglutide, there was a more pronounced increase in BMI scores in the previously treated group. This result suggests that the pharmacological benefit may be partially lost after discontinuation, reinforcing the understanding of obesity as a chronic disease rather than a condition necessarily resolved after a short period of

pharmacotherapy (KELLY et al., 2020).

This issue is even more relevant in the pediatric population because treatment initiated at age 12 or 13 can potentially extend for several years. The available trials are relatively short in duration compared to the potential duration of exposure, so questions remain regarding cumulative safety, linear growth, puberty, bone health, body composition, and the transition to adult care (KELLY et al., 2020; WEGHUBER et al., 2022).

Body composition represents a particularly important gap. Most pediatric studies use weight, BMI, or BMI z-score as primary outcomes, but these measures do not adequately distinguish between loss of adipose tissue and fat-free mass. During adolescence, a period marked by rapid acquisition of muscle and bone mass, the preservation of functional mass should be considered an additional treatment goal, rather than merely a numerical reduction in body weight (WEGHUBER et al., 2022; SEDENHO-PRADO et al., 2025).

This aspect underscores the importance of combining pharmacotherapy with multidisciplinary treatment. The reduction in energy intake induced by incretin agonists may contribute to weight loss, but it is necessary to ensure adequate intake of protein, micronutrients, calcium, and vitamin D, as well as regular physical activity and stimuli capable of preserving muscle mass and bone health (WEGHUBER et al., 2022).

Tirzepatide broadens the discussion by presenting a distinct mechanism of action. While liraglutide and semaglutide act primarily on the GLP-1 receptor, tirzepatide combines GIP and GLP-1 agonism, a strategy associated with significant metabolic and weight-related effects in adults. The possibility of replicating some of these benefits in the pediatric population has driven the development of specific studies, although directly extrapolating adult results to adolescents is not methodologically sound (HANNON et al., 2025; JASTREBOFF et al., 2025).

The SURPASS-PEDS study represents an important advance because it demonstrated that tirzepatide is biologically active and clinically effective in young people. Hannon et al. (2025) evaluated 99 participants aged 10 to under 18 years with type 2 diabetes mellitus and found a pooled mean reduction in HbA1c of 2.23 percentage points compared with an increase of 0.05 in the placebo group. In addition, BMI decreased by 7.4% with the 5 mg dose and by 11.2% with the 10 mg dose, demonstrating a substantial effect on body weight in the study population (HANNON et al., 2025).

The results of the SURPASS-PEDS study also provide initial information on the pediatric safety of tirzepatide. The most common adverse events were gastrointestinal, predominantly mild or moderate, and decreased over the course of treatment. Two participants in the 5 mg group discontinued therapy due to adverse events, and no deaths were reported, suggesting a tolerability profile consistent with that observed in adults during the study period (HANNON et al., 2025).

However, SURPASS-PEDS cannot be considered definitive proof of tirzepatide's efficacy for isolated pediatric obesity. All participants had type 2 diabetes mellitus, a condition associated with increased insulin resistance, specific metabolic abnormalities, and concomitant use of metformin and/or basal insulin. Consequently, the reduction in BMI observed in this trial should not be automatically extrapolated to adolescents with obesity who do not have diabetes (HANNON et al., 2025).

This distinction is crucial because the available data for semaglutide and tirzepatide do not have the same degree of clinical applicability. Semaglutide was evaluated directly in adolescents with obesity in the STEP TEENS trial, whereas the published pediatric evidence for tirzepatide to date derives from a population with type 2 diabetes. Thus, any comparison of superiority between the two therapies for adolescent obesity would be premature (WEGHUBER et al., 2022; HANNON et al., 2025).

Expectations regarding tirzepatide, therefore, should remain tied to studies specifically focused on adolescent obesity. The SURMOUNT-ADOLESCENTS trials were designed precisely to evaluate BMI reduction, safety, and other outcomes in adolescents with obesity or overweight associated with comorbidities, and their results will be crucial for defining the true role of dual GIP/GLP-1 therapy in this context (HANNON et al., 2025).

The increasing efficacy of these therapies also raises a conceptual question: does greater weight loss necessarily equate to better treatment? In the pediatric population, the answer must consider not only BMI reduction but also adequate growth, body composition, pubertal development, quality of life, physical functioning, and mental health. Thus, treatment goals that are overly focused on percentage weight loss may be inappropriate for developing adolescents (WEGHUBER et al., 2022).

Mental health deserves special attention. Children and adolescents with obesity are at greater risk of stigma, bullying, body dissatisfaction, and psychological distress, and any therapeutic intervention must be conducted in a way that does not reinforce a moralizing or overly aesthetic view of weight. Weight loss can improve quality of life, but therapeutic success must include psychosocial well-being and healthy eating behaviors (KELLY et al., 2020; WEGHUBER et al., 2022).

The liraglutide study reported one suicide in the treated group, which the investigator considered unlikely to be related to the medication. An isolated event does not allow for the establishment of a causal relationship, but its occurrence highlights the importance of mental health assessment and monitoring during treatment, especially in a population

where emotional disorders and obesity may coexist (KELLY et al., 2020).

The issue of age group also warrants attention. Most of the robust data focuses on adolescents, and the evidence regarding children under 12 years of age is much more limited. Recent meta-analyses indicate a reduction in BMI in children exposed to GLP-1 agonists, but emphasize that the amount of evidence is still limited and insufficient to make broad extrapolations regarding long-term safety (ROMARIZ et al., 2026).

Another challenge involves identifying patients who have the best benefit-risk ratio. Pediatric obesity is a heterogeneous condition, and adolescents with severe obesity, insulin resistance, type 2 diabetes, metabolic liver disease, or multiple comorbidities may derive greater absolute benefit from pharmacotherapy than patients with less severe forms of the disease. Future studies should evaluate clinical and metabolic predictors capable of guiding a more individualized selection (SEDENHO-PRADO et al., 2025; HANNON et al., 2025).

Contemporary meta-analyses also demonstrate that, despite the overall efficacy of the class, there is still significant heterogeneity among studies. Katole et al. (2024) reported high heterogeneity for some outcomes, while Sedenho-Prado et al. (2025) highlighted that different metabolic markers did not show a uniform response. This reinforces the need for larger trials, direct comparisons, and standardization of the outcomes used in pediatric research (KATOLE et al., 2024; SEDENHO-PRADO et al., 2025).

The cost and availability of medications may also limit their applicability in the general population. Continuous incretin therapies are costly, and the need for prolonged treatment may hinder access and adherence. In health systems with limited resources, prioritization criteria, cost-effectiveness, and equity should be considered alongside clinical efficacy and safety (SEDENHO-PRADO et al., 2025).

The risk of weight regain after discontinuation also remains a concern. Although long-term pediatric data are still limited, the increase in BMI following discontinuation of liraglutide suggests that the pharmacological effects may not be fully maintained after withdrawal. This brings the treatment of pediatric obesity closer to the concept of chronic management and reinforces the need for specific studies on maintenance, dose reduction, and discontinuation strategies (KELLY et al., 2020).

Thus, the studies by Kelly et al. (2020), Weghuber et al. (2022), and Hannon et al. (2025) can be understood as successive stages in the pharmacological evolution of incretin therapies in young people. Kelly et al. demonstrated the benefit of liraglutide; Weghuber et al. significantly enhanced weight-related efficacy with semaglutide; and Hannon et al. showed that the dual GIP/GLP-1 action of tirzepatide produces significant glycemic and weight-related effects in young people with type 2 diabetes. However, the applicability of these studies varies depending on the population studied (KELLY et al., 2020; WEGHUBER et al., 2022; HANNON et al., 2025).

The main current gaps in knowledge focus on safety during several years of exposure, effects on lean body mass and bone density, linear growth, pubertal maturation, reproductive health, eating behavior, mental health, and weight maintenance after discontinuation. For tirzepatide, there remains a need for specific Phase 3 evidence in adolescents with obesity without diabetes before any conclusions can be drawn regarding its definitive role in the treatment of pediatric obesity (WEGHUBER et al., 2022; HANNON et al., 2025).

Thus, the currently available evidence supports GLP-1 receptor agonists as effective therapies for selected adolescents with obesity, with semaglutide standing out due to the magnitude of BMI reduction demonstrated in the STEP TEENS trial. Tirzepatide shows particularly significant potential and has already demonstrated substantial clinical activity in young people with type 2 diabetes; however, its specific efficacy and safety for pediatric obesity should remain classified as emerging until trials dedicated to this population are completed (WEGHUBER et al., 2022; HANNON et al., 2025; SEDENHO-PRADO et al., 2025).

CONCLUSION

The available evidence demonstrates that GLP-1 receptor agonists represent an important advancement in the pharmacological treatment of pediatric obesity, especially in adolescents with persistent or severe obesity and an insufficient response to lifestyle interventions. Liraglutide demonstrated superior efficacy compared to placebo, while semaglutide showed a substantially greater weight reduction in the STEP TEENS trial, establishing itself as one of the most effective incretin therapies currently demonstrated specifically in adolescents with obesity (KELLY et al., 2020; WEGHUBER et al., 2022).

Semaglutide resulted in an average 16.1% reduction in BMI over 68 weeks, accompanied by improvements in parameters related to adiposity and cardiometabolic risk. These results suggest that the benefits of incretin therapies are not limited to numerical weight loss but may also contribute to improving metabolic abnormalities associated with obesity during adolescence (WEGHUBER et al., 2022).

Subsequent systematic reviews and meta-analyses have confirmed that GLP-1 agonists produce greater reductions in weight and BMI compared to placebo or lifestyle intervention alone. However, heterogeneity among trials and the lack of direct comparisons between different molecules call for caution when establishing relative superiority among the medications, despite the greater magnitude of effect observed with semaglutide in the available analyses (KATOLE

et al., 2024; ROMARIZ et al., 2026).

The safety profile identified in the studies was characterized primarily by gastrointestinal adverse events, including nausea, vomiting, and diarrhea. These events occurred more frequently among treated participants but were not accompanied by a consistent increase in serious adverse events during the evaluated periods. The occurrence of cholelithiasis observed with semaglutide reinforces, however, the need for careful clinical monitoring during significant weight loss (KELLY et al., 2020; WEGHUBER et al., 2022; SEDENHO-PRADO et al., 2025).

Long-term safety remains one of the major gaps in the literature. Children and adolescents are in phases of linear growth, pubertal maturation, bone mass acquisition, and muscle development, making an assessment based exclusively on BMI insufficient. Future studies should systematically incorporate body composition, bone mineral density, growth, pubertal development, nutritional status, reproductive health, and physical function (WEGHUBER et al., 2022; ROMARIZ et al., 2026).

Tirzepatide represents one of the main future prospects for the pharmacological treatment of pediatric obesity. The SURPASS-PEDS study demonstrated that dual agonism of the GIP and GLP-1 receptors can produce a significant improvement in HbA1c and a reduction in BMI in children and adolescents with type 2 diabetes mellitus, providing important evidence regarding the pharmacological activity and safety of tirzepatide in a pediatric population (HANNON et al., 2025).

However, the results of SURPASS-PEDS should not be interpreted as definitive proof of tirzepatide's efficacy in adolescents with obesity who do not have diabetes. The study population had type 2 diabetes mellitus and specific metabolic characteristics, making trials dedicated to obesity necessary before establishing its therapeutic role in this context (HANNON et al., 2025).

As of September 2026, the SURMOUNT-ADOLESCENTS studies, which specifically targeted adolescent obesity, remained essential for addressing this question. Thus, tirzepatide should be considered a therapy with high potential for pediatric obesity, but its specific efficacy in this population still required confirmation through dedicated Phase 3 trials (HANNON et al., 2025).

Greater pharmacological efficacy also does not eliminate the need for multidisciplinary treatment. Nutritional intervention, physical activity, preservation of lean body mass, sleep quality, family support, mental health assessment, and addressing weight-related stigma remain essential components of management; pharmacotherapy should be integrated into this care and not used as a stand-alone strategy (KELLY et al., 2020; WEGHUBER et al., 2022).

The possibility of weight regain after discontinuation represents another relevant issue. The increase in BMI observed after discontinuation of liraglutide suggests that part of the pharmacological benefit may depend on continued treatment. This finding reinforces the need to understand pediatric obesity as a chronic condition and to investigate maintenance strategies, duration of therapy, and safe methods of discontinuation (KELLY et al., 2020).

It can be concluded that GLP-1 agonists already play a significant role in the treatment of obesity in selected adolescents, with semaglutide demonstrating the greatest reduction in BMI in a clinical trial specifically designed for this population. Tirzepatide shows promising pediatric results in type 2 diabetes and has the potential to further expand the efficacy of incretin therapies; however, its specific use in pediatric obesity should continue to be guided by evolving evidence. The future of this approach will depend on striking a balance between efficacy, long-term safety, preservation of growth and development, and maintenance of the metabolic and psychosocial health of children and adolescents (WEGHUBER et al., 2022; HANNON et al., 2025; SEDENHO-PRADO et al., 2025).

REFERENCES

1. HANNON, Tamara S.; CHAO, Lily C.; BARRIENTOS-PÉREZ, Margarita; PAMIDIPATI, Karthik Chandrasekhar; FERNÁNDEZ LANDÓ, Laura; LEE, Clare J.; PATEL, Hiren; BERGMAN, Brandon K. Efficacy and safety of tirzepatide in children and adolescents with type 2 diabetes (SURPASS-PEDS): a randomized, double-blind, placebo-controlled, phase 3 trial. The Lancet, vol. 406, no. 10511, pp. 1484–1496, 2025. DOI: https://doi.org/10.1016/S0140-6736(25)01774-X.

2. JASTREBOFF, Ania M.; LE ROUX, Carel W.; STEFANSKI, Adam; ARONNE, Louis J.; HALPERN, Bruno; WHARTON, Sean; WILDING, John P. H.; PERREAULT, Leigh; ZHANG, Shuyu; BATTULA, Ramakrishna; BUNCK, Mathijs C.; AHMAD, Nadia N.; JOURAVSKAYA, Irina. Tirzepatide for obesity treatment and diabetes prevention. The New England Journal of Medicine, vol. 392, no. 10, pp. 958–971, 2025. DOI: https://doi.org/10.1056/NEJMoa2410819.

3. KATOLE, Akshay et al. The anti-obesity effect and safety of GLP-1 receptor agonists in overweight/obese adolescents without diabetes mellitus: a systematic review and meta-analysis. 2024. PMID: 39238716.

4. KELLY, Aaron S.; AUERBACH, Pernille; BARRIENTOS-PEREZ, Margarita; GIES, Inge; HALE, Paula M.; MARCUS, Claude; MASTRANDREA, Lucy D.; PRABHU, Nandana;

ARSLANIAN, Silva. A randomized, controlled trial of liraglutide for adolescents with obesity. The New England Journal of Medicine, vol. 382, no. 22, pp. 2117–2128, 2020. DOI: https://doi.org/10.1056/NEJMoa1916038.

5. PAGE, Matthew J.; MCKENZIE, Joanne E.; BOSSUYT, Patrick M.; BOUTRON, Isabelle; HOFFMANN, Tammy C.; MULROW, Cynthia D. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, vol. 372, p. n71, 2021. DOI: https://doi.org/10.1136/bmj.n71.

6. ROMARIZ, Livia M.; DE MELO, Amanda Almeida Cavalcanti; FINNEGAN, Emma; MESQUITA, Yasmin; JANOVSKY, Carolina C. Porto Silva. GLP-1 receptor agonists for the treatment of obesity in children and adolescents: a meta-analysis of randomized controlled trials. Pediatric Research, vol. 99, no. 2, pp. 502–510, 2026. DOI: https://doi.org/10.1038/s41390-025-04228-1.

7. SEDENHO-PRADO, Luis Gustavo; YUGAR, Louise Buonalumi Tacito; WHITAKER, Ana Raquel; MARTINS, Marília Paiva; JESUS, Daniel Campos; FERREIRA, Isadora Maria Castilho da Silva; SILVA, Cleide Aparecida Moreira; NADRUZ, Wilson; CERCATO, Cintia; SPOSITO, Andrei C. Metabolic outcomes and safety of GLP-1 receptor agonists in children and adolescents with obesity: a systematic review and meta-analysis. International Journal of Obesity, vol. 49, no. 8, pp. 1469–1479, 2025. DOI: https://doi.org/10.1038/s41366-025-01790-w.

8. WEGHUBER, Daniel; BARRETT, Timothy; BARRIENTOS-PÉREZ, Margarita; GIES, Inge; HESSE, Dan; JEPPESEN, Ole K.; KELLY, Aaron S.; MASTRANDREA, Lucy D.; SØRRIG, Rasmus; ARSLANIAN, Silva. Once-weekly semaglutide in adolescents with obesity. The New England Journal of Medicine, vol. 387, no. 24, pp. 2245–2257, 2022. DOI: https://doi.org/10.1056/NEJMoa2208601