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Efficacy and safety of GLP-1 Receptor Agonists for BMI Reduction in Children and Adolescents with Obesity: A Narrative Review

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Abstract

Background. Obesity arises as a global health issue, increasingly affecting children and adolescents. Excess body weight is associated with multiple metabolic risks and poor quality of life. Lifestyle therapy remains the cornerstone of weight management, the obtained effects are often modest. GLP-1 receptor agonists appear to improve BMI reduction, metabolic parameters, and present with good tolerability.

Aim. This narrative review aims to summarize and discuss the current evidence on theefficacy and safety of selected long-acting GLP-1 receptor agonists in children and adolescents with obesity.

Material and methods. A literature review was performed using the PubMed database. Studies evaluating the efficacy of using GLP-1 receptor agonists, with a focus on BMI reduction, improvement in metabolic parameters, safety, and tolerability in children and adolescents, were included in the analysis.

Results. Semaglutide appeared to be the most effective GLP-1 receptor agonist in reducing BMI and improving metabolic risk factors. Liraglutide demonstrated moderate effectiveness in body mass reduction and modest improvement in metabolic parameters, with no significant benefits observed in children with Prader-Willi syndrome. Exenatide XR showed no significant effect on BMI reduction and limited benefits in the analyzed population. The most commonly reported side effects across the studies were gastrointestinal disorders, with an overall acceptable safety profile.

Conclusions. Semaglutide and liraglutide are effective pharmacological options to support BMI reduction and improve metabolic profile in the pediatric population. Lifestyle therapy should remain the foundation of body weight reduction, supported by appropriate pharmacological treatment. Further research is needed to evaluate the long-term efficacy and safety of GLP-1 receptor agonists in the treatment of obesity in children and adolescents.

Keywords: GLP-1 receptor agonists, semaglutide, liraglutide, exenatide, obesity, metabolic risks, adolescents, children, pediatric population

1. Introduction

Obesity appears as one of the most significant public health issues that modern medicine struggles with. In the general population, frequency arises consistently, including children and adolescents. According to contemporary epidemiological data, approximately 8–9% of children and adolescents in highly developed countries meet the criteria for obesity [8]. Early onset obesity increases the likelihood of maintaining excess body weight in adulthood and promotes the development of metabolic and cardiovascular complications in the future [9]. The pathogenesis of developmental age obesity is multifactoral and consists of environmental,

genetic, behavioral, and hormonal issues. The disregulation of hunger and satiation regulation also plays a crucial role in the pathomechanism, leading to excessive energy intake [10]. Rarely, obesity may be caused by hereditary genetic disorders [5].

Obesity in children and adolescents is associated with insulin resistance, pre-diabetes, type 2 diabetes, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, orthopaedic complications, and psychosocial issues [9]. Non-pharmacological interventions remain a basis of obesity management, which include dietary modification, increased physical activity, and complex psychological support [24]. Although such interventions lead to BMI reduction, the obtained effects are usually modest [12]. When the effects of the conservative treatment are insufficient, a group of patients may require lifestyle therapy supported with pharmacotherapy. Among clinical studies involving children and adolescents, GLP-1 receptor agonists require specific attention. It is proven that some of these medications effectively reduce BMI and improve metabolic parameters.

1.1 Mechanism of action

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells in response to food intake. This specific hormone is a significant component of the entero-pancreatic axis that regulates energy homeostasis. It binds with GLP-1 receptor (GLP-1R), which induces glucose-dependent insulin secretion and suppresses glucagon secretion. Through central effect in the hypothalamus and brain stem, GLP-1R activation delays gastric emptying and causes a feeling of satiation, which results in lowered energy supply and body mass reduction. GLP-1 agonists mimic the function of the endogenous intestinal hormone. Long-acting GLP-1 analogues have been proven to reduce tissue insulin resistance and potential cardiovascular risk by reducing inflammation and improving endothelial function [25,26,27]. Drugs like liraglutide, semaglutide, and exenatide were evaluated in randomised controlled trials (RCTs) in children and adolescents with obesity.

2. Research materials and methods

2.1. Data collection and analysis

References for this narrative review were identified through searches in PubMed for articles published between January 2020 and January 2026. The research strategy included

combinations of pediatric and adolescent populations with obesity that used selected GLP-1 receptor agonists like semaglutide, liraglutide, and exenatide. Primarily selected comparators were placebo, metformin, or orlistat. The outcomes that included the comparison of Body mass index (BMI), selected metabolic parameters, and tolerability were preferred. Studies were included if the analyzed obese population was aged 6-<18 and GLP-1 receptor agonists were used as an additive treatment to lifestyle therapy. Out of 26 identified articles, five studies met the inclusion criteria and were included in this narrative review.

2.2. AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Evidence from randomized controlled trials

All analyzed studies were randomized controlled trials in which participants were assigned to a treatment or placebo group in a 1:1 or 2:1 ratio. In each study, the lifestyle therapy was an obligatory element besides the pharmacological treatment.

3.1.1. Semaglutide in adolescents

In the STEP TEENS trial, Weghuber et al. investigated the efficacy of semaglutide in adolescents with obesity or overweight with at least one weight-related comorbidity. The mean baseline BMI were 37,7±6,7 in the semaglutide group and 35,7±5,4 in the placebo

group. After 68 weeks of evaluation, the change of BMI was -16,1% in the semaglutide group compared with +0,6% in the placebo group [1].

3.1.2. Exenatide XR in adolescents

In a randomized controlled trial, Fox et al. evaluated the efficacy of Exenatide XR in adolescents with obesity. Participants underwent strict lifestyle therapy before randomization, where 5% BMI reduction was required. The mean BMI at the randomization point was 36.9±4.4. After 52 weeks period, mean BMI increased 4.6% and 10.1% in the exenatide XR and placebo groups, respectively [3].

3.1.3. Liraglutide in adolescents

In SCALE TEENS, Kelly et al. analyzed the efficacy of liraglutide in adolescents with obesity, with or without a diagnosis of type 2 diabetes. The mean baseline BMI were 35,3±5,1 in the liraglutide group and 35,8±5,7 in the placebo group. After 56 weeks of treatment, the change of BMI was -4,6% in the liraglutide group vs -0,6% in the placebo group. During the follow-up period up to week 82, BMI rebound was observed in both groups [2].

3.1.4. Liraglutide in children

In another RCT, Fox et al. investigated the efficacy of liraglutide in children aged 6-<12 with obesity. The trial consisted of 56 weeks of treatment followed by 26 week follow-up period. At week 56, the mean percentage change in baseline BMI was −5.8% in the liraglutide group compared with +1.6% in the placebo group. At week 82, the changes in baseline BMI were -0,8% in the liraglutide group and +6,7% in the placebo group, respectively [4].

3.1.5. Liraglutide in children and adolescents with Prader – Willi Syndrome (PWS)

Diene et al. investigated the efficacy of liraglutide in children and adolescents with Prader-Willi syndrome (PWS), a genetic disorder caused by the loss of function in paternally derived genes on chromosome 15. The study included a 16-week double-blind period followed by 52 weeks

of unblinded liraglutide treatment. The base point BMI in adolescents was respectively 36.3 ± 6.5 in the liraglutide group and 40.2 ± 10.7 in the placebo group, while in children it was 32.4 ± 7.5 and 30.3 ± 5.5, respectively. At week 16, the differences in BMI-SDS between liraglutide and placebo were −0.07 in adolescents and −0.06 in children. After 52 weeks, the changes were −0.14 in adolescents and −0.07 in children [5].

Study	**BMI change – treatment**	**BMI change – placebo**	**Statistical significance**
STEP TEENS (Semaglutide) Weghuber et al.	−16.1%	+0.6%	+
Exenatide XR Fox et al.	+4.6%	+10.1%	+
SCALE TEENS (Liraglutide) Kelly et al.	−4.6%	−0.4%	+
Liraglutide 6–<12 Fox et al.	-5.8%	+1.6%	+
Liraglutide (PWS – adolescents)* Diene et al.	−0.14 (BMI SDS)	−0.07 (BMI SDS)	−
Liraglutide (PWS – children)* Diene et al.	−0.07 (BMI SDS)	−0.03 (BMI SDS)	−

Table 1. BMI change in pediatric population in GLP-1 receptor agonists RCTs. Values are presented as reported in the original research.

* Results reported as BMI standard deviation score (BMI SDS) as in original study instead of percentage change

4. Discussion

4.1. Clinical relevance of BMI reduction in pediatric population

Obesity in the pediatric population is diagnosed when body mass index (BMI) exceeds the 95th percentile for sex and age [7]. Clinical studies evaluating the efficacy of GLP-1 receptor agonists proved the major significance of semaglutide and liraglutide in BMI reduction. The magnitude of BMI reduction with semaglutide appears comparable to results reported in adult clinical trials [13]. There are several reasons for the importance of reducing excessive

body weight. The primary goal of the treatment is to minimize the risk of developing serious obesity-related complications. Early intervention may prevent the development or lead to potential remission of conditions such as type 2 diabetes, dyslipidemia, NAFLD, hypertension, atherosclerosis, heart failure, and certain types of cancer. The quality of life may improve, and the risk of impairment and premature mortality decreases [15].

4.2. Additional evidence on efficacy

4.2.1. Metabolic effects

Following clinical studies showed varying degrees of effects in metabolic profile improvement. Analyzed parameters included fasting plasma glucose, glycated hemoglobin, fasting insulin, waist circumference, systolic and diastolic blood pressure, lipid profile, and triglycerides. Among adolescents aged 12 - <18, semaglutide showed mild to essential improvement in each parameter. Liraglutide demonstrated modest to moderate glycemic and cardiometabolic improvements. In comparison, exenatide treatment resulted only in significant improvement of the TG/HDL-c ratio with limited effects on other metabolic parameters. In younger patients aged 6 - <12, liraglutide therapy achieved mild improvement in waist circumference and blood pressure.

In following studies, treatment with GLP-1 receptor agonist was associated with a minor increase in heart rate in comparison to placebo. In experimential study on an animal model, Lubberding et. al discovered that the chronotropic effect of GLP-1 agonist acts through GLP-1R in pacemaker cells in the sinus node. This specific observation requires further investigation in humans [6].

4.2.2. Psychological well-being

Another important aspect in obese pediatric populations is the effect of the treatment on psychological well-being. Psychological outcomes were analyzed on the SCALE TEENS, Exenatide XR trial, and the STEP TEENS using the Impact of Weight on Quality of Life – Kids (IWQOL-Kids) questionnaire. Semaglutide was the only GLP-1R agonist with significant improvement in self-esteem and psychological well-being. However, none of the following studies reported significant psychiatric side effects or deterioration in mental health status during treatment.

Study:	**STEP TEENS (Semaglutide)**		**Exenatide XR****		**SCALE TEENS (Liraglutide)**		**Liraglutide children 6-<12**	
Change in selected characteristics:	**S**	**P**	**E**	**P**	**L**	**P**	**L**	**P**
Systolic blood pressure (mm Hg)	-2,7	-0,8	+4	+7	-1,21	+0,84	-1,7	+1,7
Heart rate (bpm)	+1,2	-2,3	+8	+1	+1,87	-0,14	+0	-4
Waist circumference (cm)	-12,7	-0,6	No data	No data	-4,35	-1,42	-2,0	+1,3
HbA1C (%)	-0,4	-0,1	+0,2	+0,1	-0,1	-0,03	-0,2	-0,1
Total Cholesterol (mg/dl)	-8,3	-1,3	+19,9	+15,3	+1,0	+0,99	No data	No data
Triglycerides (g/dl)	-28,4	+2,6	+5,3	+19	+0,92	+0,93	No data	No data
Total IWQOL–Kids questionnaire score	+5,3	+1,0	-1,7	+4	+7,88	+6,57	No data	No data

Table 2. Comparison of selected metabolic and lifestyle effects of analyzed GLP-1 receptor agonists. Values are presented as reported in the original studies.

*Liraglutide in PWS patients study was excluded from the table due to no specific data on following selected characteristics in original study

**Exenatide XR data was collected 52 weeks after randomization, following a ≥5% BMI reduction during run-in phase

Table legend: S – semaglutide; L – liraglutide; E – Exenatide XR; P - Placebo

4.3. Safety and tolerabilty

4.3.1. The most common adverse reactions

Adverse reactions are an inevitable part of drug therapy. The most common side effects reported across the analyzed clinical studies were gastrointestinal disorders, including nausea, vomiting, diarrhea, abdominal pain, and constipation. The prevalence was associated with dose escalation toward the maximum therapeutic dose. These adverse events led some patients to discontinue the therapy or prevented them from reaching the maximum dose. This group of symptoms was more frequent and more pronounced in the GLP-1 receptor agonist groups, especially in the liraglutide group among children aged 6 to <12. Although the overall percentage of reported adverse events was similar between treatment and placebo groups.

4.3.2. Rare and severe side effect

A few patients in STEP TEENS and SCALE TEENS trials suffered from cholecystitis. Rapid body mass loss is a known risk factor for gallstone disease [20]. One case of acute pancreatitis was reported during liraglutide therapy, although a mild asymptomatic increase in amylase and lipase blood levels was observed more frequently. Serious adverse events were uncommon and occurred similarly in treatment and placebo groups.

In the study where children with Prader-Willi Syndrome were evaluated, three episodes of clinically significant hypoglycemia were reported in the liraglutide group – this finding may be related to adrenal insufficiency and GH deficiency commonly observed in patients with PWS [21].

None of the analyzed studies reported significant disturbances in pubertal development. Similarly, no significant effect on the pubic stage was observed.

Study:	STEP TEENS (Semaglutide)		Exenatide XR		SCALE TEENS (Liraglutide)		Liraglutide children 6-<12		Liraglutide (PWS)	
Selected adverse events:									A/C	A/C
	S	P	E	P	L	P	L	P	L	P
Gastrointestinal disorders (% of participants)	62	42	* ≥39 %	* ≥21 %	64,8	36,5	80	54	55/58,8	41,7/28 ,6
Increase in pancreatic enzymes	+	-	No data	No data	No data	No data	+	-	No relevant change	No relevant change
Pancreatitis (n)	0	0	No data	No data	1	0	No data	No data	0	0
Gallbladder disease (n)	5	0	No data	No data	0	1	No data	No data	No data	No data
Clinically significant hypoglycemia (n)	0	0	No data	No data	0	0	No data	No data	2/1	0/0
Serious adverse reaction (n)	15	6	1	0	3	5	7	2	3/5	3/1
Premature discontinuations (n)	6	3	3	7	13	0	6	0	2/1	0/0
Fatal adverse events (n)	0	0	0	0	1**	0	0	0	0/0	0/0

Table 3. Comparison of selected adverse events of analyzed GLP-1 receptor agonists. Values are presented as reported in the original studies.

*No specific data was given; used percentage values refer to most common gastrointestinal side effect which was nausea

**One suicide was reported; according to the authors was unlikely related to trial treatment

Table legend: S – semaglutide; L – liraglutide; E – Exenatide XR; P – Placebo; n – number of participants; A/C – Adolescents/Children

4.4. Genetically Determined Obesity

In children with Prader-Willi Syndrome, the liraglutide treatment did not cause significant BMI reduction compared with other studies. This may suggest that GLP-1 receptor agonists may be less effective in obesity driven by hypothalamic dysfunction. However, the analyzed study

reduced hyperphagia total and drive scores in adolescents treated with liraglutide. Some positive effect on BMI and glycemic profile was shown in several case reports among adults with semaglutide, but the effects on patients were diversified [16,17]. Further investigation on the use of GLP-1 receptor agonists on PWS patients is advised.

4.5. Limitation of current evidence

The number of studies investigating the use of GLP-1 receptor agonists in the pediatric population is currently limited. This may be a result of the relatively short time of accessibility of these agents for children and adolescents with obesity.

The efficacy has been studied more in adults, where GLP-1 receptor agonists have been gaining additional indications and have been widely analyzed and reported with more long-term results on efficacy or side effects [22]. Small research groups, heterogeneous design of the studies, and a limited number of meta-analyses do not allow for a precise evaluation of efficacy, safety, and possibilities for recognising specific indications to begin GLP-1R agonist therapy.

Long-term data on the safety in children and adolescents is limited, regarding the risks of gallbladder diseases, pancreatitis, suicidal ideation, and disordered eating [18,19]. A limited number of real-life analyses on GLP-1 agent treatment in the pediatric population may be related to the high monthly cost of treatment, which leads to discontinuation of the treatment after a few months [23].

4.6. Future directions

Anti-obesity medications represent a new therapeutic direction in the treatment of lifestyle-related diseases. GLP-1 agonists take the primary target, but currently, only short-term data on their efficacy and safety are available in the pediatric population.

Those agents were initially developed for the treatment of type 2 diabetes; due to their pharmacological features, they have gained recognition in obesity treatment [14]. Ongoing development of new agents, including oral semaglutide, may provide new therapeutic opportunities and improve general health and quality of life [11]. Among adults, an increasing

number of data and analyses on safety and long-term efficacy are widely available. Similar analyses are required in the pediatric population. Further research focused on the comparison of GLP-1 receptor agonists and other pharmacological treatments that are used to support obesity management is also required.

Important clinical questions remain unresolved, including the optimal and safest age for initiating the therapy, the minimal required sustaining therapy time, and risk factors for serious adverse effects that need to be determined, based on complex patient profile evaluation. Long-term follow-up studies on adults who were treated with GLP-1 agonists during childhood or adolescence are also necessary in the future.

5. Limitations of study

The study has several limitations. Primarily, it is not a systematic review and does not follow a strictly defined protocol for study selection, comprehensive database searching, and assessment of potential selection bias. The analyzed studies were heterogeneous in design, including different methods of comparison of the results, unequal ratios between treatment and placebo groups, and varying reported results in metabolic parameters. Moreover, the studied populations were relatively small, which limited a broad evaluation.

6. Conclusions

Among the analyzed studies, semaglutide appeared to be the most effective agent to reduce BMI and metabolic risks. Liraglutide demonstrated moderate effectiveness in most analyzed trials, except the study involving PWS patients. Exenatide XR demonstrated a mild increase in BMI from the randomization procedure, with limited metabolic benefits compared to semaglutide and liraglutide.

GLP-1 receptor agonists appear as safe treatment with an acceptable safety profile in pediatric obesity trials. Gastrointestinal disorders were the most common adverse effects; they were generally dose-dependent and mostly mild to moderate in severity. Serious adverse effects and reactions were rare.

Nevertheless, bear in mind that treatment of obesity requires constant specialised care and an individualized approach based on lifestyle therapy and psychological support. Awareness of excessive body mass consequences is fundamental for effective treatment. The choice of therapy should be based on a thorough medical interview that assesses the probability of compliance and adherence. Further research is required to evaluate the efficacy and safety of GLP-1 receptor agonists in the treatment of obesity in children and adolescents. The take-home message is to remember that the pharmacological approach should be considered only as an addition to body mass reduction. The foundation of body weight reduction should remain the lifestyle therapy and awareness of obesity's consequences [24].

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Data curation: JP, RM

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Chat GPT (OpenAI) to improve grammar and language corrections. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility fort he substantive content of the publication.

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