

Usage of Glucagon-Like Peptide-I for Obesity in Children; Updated Review of Clinicaltrials.gov

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Background: Obesity in both adults and children is a primary health concern that can lead to many complications at a young age, including insulin resistance, type 2 diabetes, and other diseases. Glucagon-like peptide-1 receptor agonists (GLP-1) are drugs utilized to treat diabetes, but they are also approved as an adjunct to a low-calorie diet to reduce body weight and to enhance the metabolic profile readings for diabetic and non-diabetic patients. However, their efficacy and safety in children have not been extensively examined.

Aim: To identify glucagon-like peptide-1 medications for obesity in pediatric participants (aged up to 17 years old).

Methods: Analysis of all clinical trials registered on ClinicalTrials.gov for obesity using GLP-1 as a treatment for children.

Results: As of January 26th, 2023, 10,828 clinical trials were found. The search included childhood obesity using GLP-1. The number of trials on the use of GLP-1 to treat childhood obesity is limited. The final number of analyzed trials was 19. GLP-1 has been shown to result in the effective management of body gain among children.

Conclusion: Exenatide, semaglutide, and liraglutide were the only GLP-1 medications used as the pharmacotherapy option. It has been studied in many circumstances eg, to treat children with severe obesity, PCOS, hypothalamic obesity, glucose tolerance, and as a complementary treatment alongside behavior-lifestyle change and surgery for obesity.

Keywords: obesity, GLP-1, clinical trials, exenatide, semaglutide, liraglutide

Introduction

Obesity in both adults and children is a primary health concern and a number of complications can arise from the condition at a young age, such as insulin resistance, type 2 diabetes mellitus (DM), and other diseases.¹ Obese children are more likely to experience hypertension, hyperlipidemia, liver and kidney diseases, cardiovascular disease, asthma, sleep apnea, and bone and joint problems.^{2,3} Obesity in pediatrics not only affects physical health, but mental health is also affected.⁴⁻⁶ Obese and overweight children are also more likely to experience bullying, depression, social isolation, and struggles with self-esteem than children of normal weight.^{7,8} The prevalence of obesity has been linked to low levels of physical activity, a poor diet and a generally sedentary way of life.⁹⁻¹¹ Additionally, many pre-packaged and processed foods are high in calories and low in nutrients, making it easier for people to consume excess calories and gain weight.^{12,13}

Therapeutically, glucagon-like peptide-1 receptor agonists (GLP-1) are employed to treat diabetes but they have also been approved as an adjunct to a lower calorie diet to reduce total body weight, and to enhance the metabolic profile readings for diabetic and non-diabetic patients.¹⁴⁻¹⁶ Their mechanism of action is that they act like GLP-1 by binding GLP-1 receptors in several tissues, for example, pancreatic beta cells, pancreatic ducts and gastric mucosa.¹⁵ Their main effect is the stimulation of the release of glucose-dependent insulin from pancreatic islets decreasing glucagon secretion in a glucose-dependent manner.¹⁷ As they slow down gastric emptying, they promote satiety, thereby reducing the number of calories consumed.^{18,19} They also increase the activity of lipolysis in adipocytes, leading to increased fat

metabolism and reduced fat storage in the body.^{20,21} This can lead to weight loss, improved insulin sensitivity, and improved metabolic profile readings.^{22,23}

However, the efficacy and safety of this drug for children have not been extensively examined. Turning to the situation of pediatrics and obesity, the World Health Organization (WHO) reported that around 39 million children aged less than 5 years old were overweight or obese in 2020. Furthermore, in 2016, among the global population of children and adolescents (aged between 5 and 19 years old), more than 340 million were obese or overweight.²⁴

Human studies have been performed to assess the effects of GLP-1 drugs on obesity, a consequence of engaging in obesity-related behaviors or being obese. A few clinical trials have been performed with children, and this paper analyzes the usage of GLP-1 with obese children.

Methods

Clinical Trials Data

The search process involved conducting a comprehensive exploration of clinical trials registered on the ClinicalTrials.gov database up to and including the date of 26th January 2023. To identify relevant studies, we utilized the keyword “Obesity” as the criterion for the “condition and disease” category within the search engine.

Data Screening and Extraction

The studies related to GLP-1 usage in obese children were screened by using database filters. “Child (birth-17)” was used as an eligibility criterion to select only the trials conducted with children. Then, “Glucagon-Like Peptide 1” was selected for the next step for the drug intervention, located on the topic tab. Exclusion criteria were used to continue the screening. Non-GLP-1 agonist drug usage and “no-results shown” were used as exclusion criteria. Eight studies passed the screening as they involved children and the use of a GLP-1 agonist. Prisma flow diagram of search identified from Clinicaltrials.gov bases presented in [Figure 1](#).

Data and information from the trials were extracted and categorized to show their trends and characteristics. The issues for categorization were title of clinical trial, drug used, condition, number of sample (n), phase of study, involvement in obesity and the rationale for GLP-1 usage were shown in [Table 1](#). Pharmacological class, indication, and the side effects of the GLP-1 agonists used were tabulated in [Table 2](#). Rationales for GLP-1 Usage in these trials were fully explained in [Table 3](#).

Results

The clinical trials registered up to and including 26th January 2023 on the ClinicalTrials.gov database was searched, using “Obesity” as the keyword for “condition and disease” in the search engine. In total, 10,828 studies related to obesity were found. This effectively located the relevant clinical trials and allowed the researchers to quickly identify studies on the topic of interest.

Drugs Used to Treat Obesity in Children

Nineteen studies were found, but only three drugs were used. These are detailed below.

1. Exenatide, which is a drug that activates GLP-1 receptors, was authorized by the US Food and Drug Administration (FDA) in 2005 to help adults with type 2 DM to improve their glycemic control in combination with diet and exercise.^{26,27} Its mechanism is similar to that of other GLP-1 receptor agonists. By attaching to GLP-1 receptors in the pancreas, it triggers a rise in the glucose-dependent release of insulin from beta cells, inhibiting glucagon secretion, slowing down the emptying of the stomach, and decreasing food consumption.^{28,29} In terms of side effects, the most common is nausea; this varies with the dosage and is becomes less common with continuous use of the drug.³⁰ Other less common side effects are vomiting, diarrhea, hypoglycemia, feeling dizzy, headaches, pruritus or nodules at the injection site, and dyspepsia.^{31–33} Moreover, exenatide itself is teratogen class C and cannot be used in pregnancy.²⁶ With regard to the incidence of hypoglycemia when taking exenatide, it is lower than with other diabetic therapies, due to the glucose-dependent release of insulin.^{34,35}

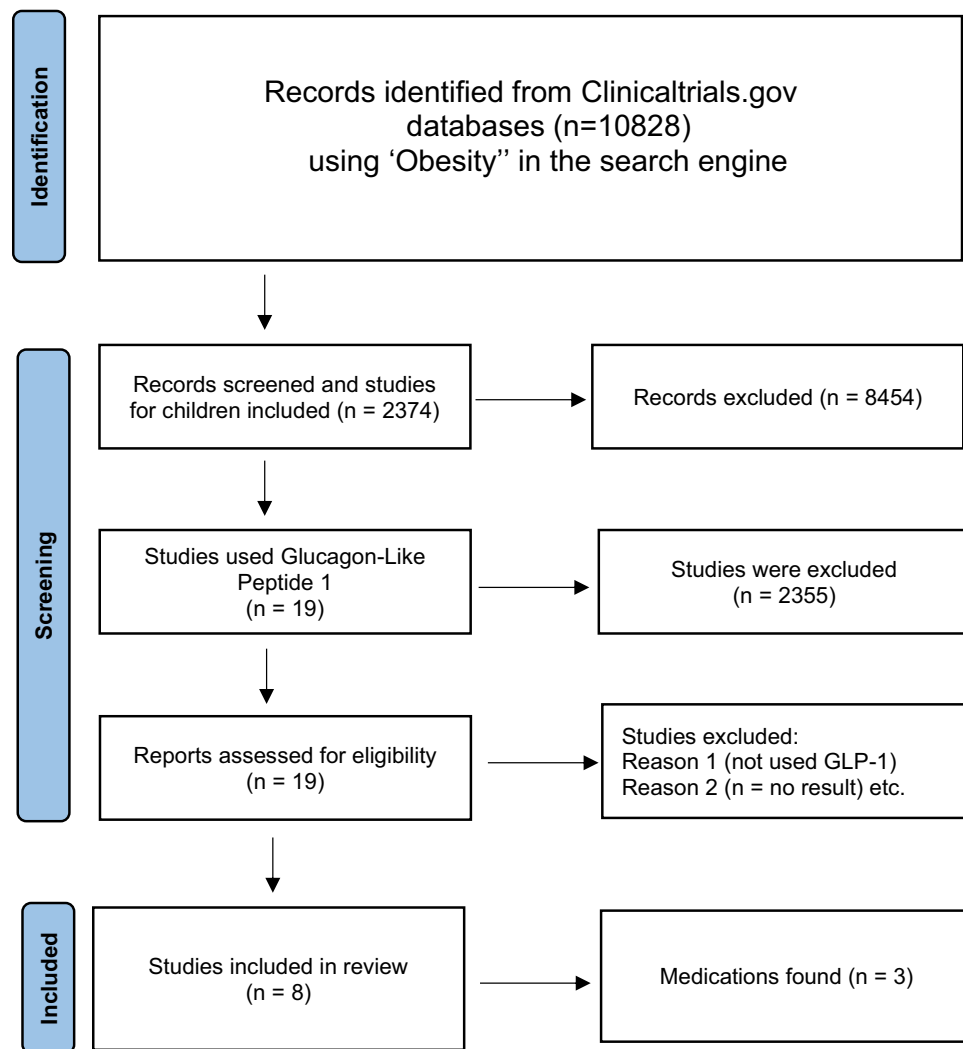


Figure 1 PRISMA flow chart of studies via Clinicaltrials.gov databases (Updated on 24th January 2022).

Notes: Adapted from BMJ (OPEN ACCESS) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow et al The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.²⁵

2. Semaglutide is a drug that stimulates GLP-1 receptors and is recommended as a supplementary treatment along with diet and exercise to enhance glycemic regulation in adults diagnosed with type 2 DM.¹⁵ It was approved in 2017 by the US FDA under the trade name of “Ozempic”. “WEGOVY” has been granted approval as a supplementary therapy along with a decreased calorie intake and increased physical activity to promote long-term weight control among adult patients who have an initial BMI ≥ 30 kg/m² (obesity) or ≥ 27 kg/m² (overweight) in combination with at least one comorbid condition associated with weight gain (such as dyslipidemia, hypertension, or type 2 DM).^{36–38}

Semaglutide is a GLP-1 analog with 94% sequence homology to human GLP-1.³⁹ Similar to other GLP-1 receptor agonists, it functions by specifically attaching to and stimulating the GLP-1 receptor. This interaction prompts pancreatic beta cells to produce more insulin and reduce glucagon secretion, ultimately resulting in a decrease in blood glucose levels.^{40,41} The blood-glucose-lowering mechanism also lengthens gastric emptying in the early postprandial phase.⁴² Moreover, the drug can also activate brain GLP-1 receptors, which physiologically regulate appetite and the intake of calories.⁴³

Table 1 Clinical Trials, Drug Used, Condition, Enrolment Size and Clinical Phase

	Clinical Trial	Drug Used	Condition	n	Phase
1	Enhancing Weight Loss Maintenance With GLP-1RA (BYDUREON™) in Adolescents With Severe Obesity	Exenatide	Severe obesity	100	2
2	Energy Balance & Weight Loss in Craniopharyngioma-related or Other Hypothalamic Tumors in Hypothalamic Obesity	Exenatide	Hypothalamic obesity	18	3
3	GLP-1 Therapy for Weight Loss and Improved Glucose Tolerance in Obese Children	Exenatide	Obesity, morbid obesity	12	2
4	Treating PCOS With Semaglutide vs Active Lifestyle Intervention	Semaglutide	Adolescent obesity	50	2
5	The Effect of GLP-1 Agonists Versus OCs on Reproductive Disorders and Cardiovascular Risks in Overweight PCOS	GLP-1 with metformin	Obesity	30	4
6	Brain Activation and Satiety in Children 2	Exenatide	Childhood obesity	64	3
7	Effect of Liraglutide on Weight Loss in Patients Who Have Undergone Revisional Bariatric Surgeries	Liraglutide	Morbid obesity	60	Not applicable
8	Liraglutide (Saxenda(R)) in Adolescents With Obesity After Sleeve Gastrectomy	Liraglutide	Obesity	50	2

Table 2 Main GLP-1 Drugs Used, Indication, and Common Side Effects

Drug Used	Indications	Common Side Effects
Exenatide	In conjunction with diet and exercise to improve glycemic control in adults with type 2 DM.	Nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, hypoglycemia.
Semaglutide	<ul style="list-style-type: none"> • Ozempic® - in conjunction with diet and exercise to improve glycemic control in adults with type 2 DM. • WEGOVY® - in conjunction with a reduced calorie diet and increased physical activity for chronic weight management in adult patients. 	Nausea, diarrhea, vomiting, constipation, pain in the abdomen, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 DM.
Liraglutide	<ul style="list-style-type: none"> • Victoza® - in conjunction with diet and exercise to improve glycemic control in adults with type 2 DM. • Saxenda® - in conjunction with a reduced calorie diet and increased physical activity for chronic weight management in adult patients. 	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, lessened appetite, dyspepsia, fatigue, dizziness, pain in the abdomen, increased lipase, and thyroid C-cell tumors.

Common side effects of semaglutide are vomiting, nausea, diarrhea, constipation, abdominal distension, abdominal pain, headache, dizziness, fatigue, dyspepsia, eructation, hypoglycemia in patients with type 2 DM, gastroenteritis, flatulence, and gastroesophageal reflux disease.^{44–46} There are concerns and safeguards associated with thyroid C-cell tumors, acute pancreatitis as observed in clinical studies, sudden gallbladder disease, hypoglycemia when taken with an insulin secretagogue or insulin, sudden kidney injury, the onset of complications related to diabetic retinopathy in individuals with type 2 DM, and suicidal ideation and behavior.⁴⁷

3. Liraglutide stimulates GLP-1 receptors and it is approved for glycemic control in children with type 2 DM (US FDA approval 2019).⁴⁸ The drug with the trade name “Victoza” is approved for this indication. In the year 2014, the FDA approved “Saxenda”, an alternative brand of liraglutide. It is used in conjunction with a calorie-restricted diet and increased physical activity for the long-term management of adult weight.⁴⁹ Liraglutide is a synthetic

Table 3 Rationale for GLP-I Usage

Drug	Involvement in Obesity	The Rationale for GLP-I Usage
Exenatide	Enhancing Weight Loss Maintenance	Improve glucose tolerance. Induction of weight loss by lowering appetite and the rate at which food moves through the digestive system. For severely obese children and obesity caused by the Prader-Willi Syndrome (PWS).
Metformin-Glp-I combination	Evaluate the effect of metformin-GLP-I Receptor agonist combination versus metformin-Diane-35 combination treatment on lipid metabolism and cardiovascular risks	GLP-I receptor agonists lower blood sugar and control weight by reducing food intake and inhibiting gastric emptying. PCOS patients who are overweight might benefit from this treatment.
Semaglutide	Examine semaglutide's effect on metabolic syndrome reduction, especially improving insulin sensitivity and lowering hepatic fat	The combination of testosterone and obesity in obese patients with polycystic ovarian syndrome can increase metabolic diseases such as fatty liver disease and insulin resistance.
Liraglutide	Evaluate the effect of liraglutide on additional weight loss after bariatric surgery	Severe obesity is treated with metabolic bariatric surgery. The majority of adolescents who undergo this surgery still have obesity 1 year later. Liraglutide combined with surgery was studied to assess its effect.

human GLP-1 receptor agonist that is acylated and shares 97% of its amino acid sequence with the natural human GLP-1.^{50,51} It functions in a similar way to endogenous GLP-1. Liraglutide attaches to the GLP-1 receptor, which is present on the cell surface, and prompts its activation. Despite being similar to natural GLP-1, liraglutide has a unique property - it is resistant to degradation by dipeptidyl peptidase 4 (DPP-4) and neutral endopeptidases (NEP). This resistance allows it to have a long plasma half-life of 13 hours when administered subcutaneously.⁵² Adverse effects that are frequent and reported in 5% or more of the cases treated with liraglutide include: vomiting, nausea, hypoglycemia, diarrhea, constipation, headache, dizziness, lessened appetite, dyspepsia, abdominal pain, tiredness, and increased lipase. Moreover, the drug label for liraglutide contains warnings and precautions related to several potential adverse effects such as thyroid C-cell tumors, acute pancreatitis, acute gallbladder disease, significant hypoglycemia when used with insulin secretagogues like sulfonylurea, increased heart rate, renal dysfunction, and suicidal thoughts and behaviors.^{53,54}

Discussion

Obesity is preventable and researchers want to explore the effects of GLP-1 in lowering body weight, body fat and improving metabolic features among pediatric participants.⁵⁵ This study evaluates the efficacy of this medication as a possible treatment approach for childhood obesity. As expected, the reasons for GLP-1 usage for obesity were involved with its mechanism and GLP-1 receptor activity, especially its non-glycemic effects and its benefits regarding comorbidity related with insulin resistance.^{30,56,57} These have a significant impact on weight loss. Its non-glycemic effects include its impact on gastric emptying time, the suppression of inappropriate post-meal glucagon elevation, and food intake reduction; all of these directly and positively impact weight loss.^{58,59}

Gastric emptying time has an effect on satiety. Previous studies have found a correlation between the duration of satiety and gastric emptying time for a solid meal. An increase in the gastric emptying rate might reduce the intake of satiety-enhancing food or caloric intake, and promote obesity.^{60,61} Therefore, the control of food or energy intake and food timing is a prominent factor in the success of weight loss therapy.⁶² Publications reveal that the glucagon level can induce satiety.^{63,64} Thus, the suppression of inappropriate post-prandial glucagon affects satiety reduction, influencing weight loss. The suppression of glucagon is the result of physiological control by insulin levels – insulin inhibits glucagon

secretion.^{65,66} Therefore, GLP-1 which enhances insulin secretion, can lead to the effect of postprandial glucagon release and satiety.⁶⁷

Turning to the insulin-related effects of GLP-1, it enhances insulin secretion and also affects insulin resistance through its effects, such as increasing the expression of glucose transporters in insulin-dependent tissues, and playing a role in lipid metabolism modulation, inflammation, and oxidative stress reduction.^{68–70} GLP-1 can also improve some comorbidities like polycystic ovary syndrome (PCOS).^{71,72} It draws attention to the study of GLP-1 and its effect on weight loss in PCOS patients, glucose tolerance, and hypothalamic obesity, as shown in the results section of this review article.

According to the results section, one main observation is that all of these studies were focused on the use of GLP-1 as a treatment for severe obesity, obesity with comorbidity, and in combination with other therapy strategies like surgery. This corresponds to the clinical recommendation in practice guidance for the treatment of childhood obesity treatment, such as the latest guidance from the American Academy of Pediatrics.

The consensus recommendation suggests that obesity weight loss pharmacotherapy can be provided to children aged 8–11 in combination with healthy behavior and lifestyle. The selection of which drug to utilize for childhood obesity may be based on medications' indications, risks, and benefits.⁷³ Although intensive health behavior and lifestyle (IHBLT) has the largest amount of supporting evidence and is the first-line recommendation, pharmacotherapy is employed for children and young people who require an extra treatment option to manage their obesity – especially children with life-threatening or simultaneous medical conditions, and those who are dealing with more pronounced obesity.⁷³

According to the guidance, the evidence on the drugs used for childhood obesity treatment is limited. However, GLP-1s, such as liraglutide, exenatide, dulaglutide, and semaglutide, are mentioned in the guidance. The weight loss effects of GLP-1 are related to its mechanism of reducing appetite by decreasing the rate at which the stomach empties and by affecting specific areas in the central nervous system. Two small studies on exenatide (by weekly injection) in 8-year-old children demonstrated a lowering of BMI by 0.9 to 1.18, but there were significant negative side effects. Exenatide is currently approved in children 10 to 17 years of age with type 2 DM. In a recent randomized controlled study, administering liraglutide injections once a day was proven to be more efficient than a placebo in reducing the weight of children aged 12 or above with obesity who had not responded to lifestyle interventions. Nonetheless, the primary drawbacks were feelings of nausea and vomiting. Also, for individuals with a family history of multiple endocrine neoplasia, there is a slightly heightened risk of developing medullary thyroid cancer.⁷³ It is obvious that pharmacotherapy can be an adjunct when behavior and lifestyle changes do not work, and drug treatment should be selected based on the cause of obesity, the presence of comorbidity, the severity of the disease and individual risk-benefit of use.

Limitations

It is important to note that the presented analysis has some limitations since the data came only from registered trials on ClinicalTrials.gov.

Conclusion

From the ClinicalTrials.gov data, it was found that GLP-1 drugs such as exenatide, semaglutide, and liraglutide were used as the pharmacotherapy option for childhood obesity. However, there is limited evidence as only eight clinical trials were conducted with a pharmacotherapy treatment for childhood obesity. It can be concluded that GLP-1 is the most common drug used for this case. The severity, comorbidity, and causes of disease are the main rationale for drug use, and drugs are usually combined with another treatment strategy such as lifestyle changes and/or surgery. The usage of GLP-1 in obesity with comorbidity and with some causes of obesity such as PCOS, hypothalamic obesity, and insulin tolerance were studied. The reason for choosing GLP-1 to treat obesity in this group is the benefit gained from the pathology related to the GLP-1 mechanism and activity.

Future Considerations

GLP-1 therapies should be used as an adjunct to lifestyle modifications, and healthcare professionals should be aware of the available GLP-1 therapies, their mechanisms of action, dosing regimens, and safety profiles. Long-term safety and efficacy data are limited, emphasizing the need for cautious monitoring and further research in this area. Future studies should focus on optimal dosages, treatment duration, and potential effects on growth and development. These guidelines aim to assist healthcare professionals in making informed decisions while considering the unique characteristics of each patient.

Disclosure

The authors report no conflicts of interest in this work.

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