GRELEWICZ, Olga, JUŚKIEWICZ, Adam, SERVAAS, Elwira, HABER, Mateusz, KULA, Paula, KOTULA, Alicja, CZACHOR, Adrianna and KUCY, Natalia. Potential of GLP-1 Analogs in Managing Hyperphagia and Obesity in Prader-Willi Syndrome: A Review of Efficacy and Safety. Quality in Sport. 2024;25:54915. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.25.54915
https://apcz.umk.pl/QS/article/view/54915

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.09.2024. Revised: 19.09.2024. Accepted: 11.10.2024. Published: 14.10.2024.

Potential of GLP-1 Analogs in Managing Hyperphagia and Obesity in Prader-Willi Syndrome: A Review of Efficacy and Safety

Olga Grelewicz*

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warszawa

olga.grelewicz@gmail.com

https://orcid.org/0000-0001-5738-9262

Adam Juśkiewicz

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warszawa

ad.juskiewicz@gmail.com

https://orcid.org/0000-0001-9884-3513

Elwira Servaas

National Medical Institute of the Ministry of the Interior and Administration, Wołoska 137, 02-507 Warszawa

servaaselwira@gmail.com

https://orcid.org/0009-0004-8432-7824

Mateusz Haber

Central Clinical Hospital in Warsaw

Banacha 1a, 02-097, Warszawa

mhaber.mateusz@gmail.com

https://orcid.org/0009-0002-8441-4931

Paula Kula

Central Clinical Hospital in Warsaw,

Banacha 1a, 02-097, Warszawa

paulakula98@gmail.com

https://orcid.org/0009-0004-7503-2602

Alicja Kotula

Infant Jesus Clinical Hospital UCC MUW,

Lindleya 4, 02-005 Warszawa

kotulaalicja5@gmail.com

https://orcid.org/0009-0008-9718-1667

Adrianna Czachor

Infant Jesus Clinical Hospital UCC MUW,

Lindleya 4, 02-005 Warszawa

adriannaczachor@gmail.com

https://orcid.org/0009-0001-8596-9341

Natalia Kucy

Infant Jesus Clinical Hospital UCC MUW,

Lindleya 4, 02-005 Warszawa

tusia.noelle@icloud.com

https://orcid.org/0009-0007-5468-6289

*corresponding author: Olga Grelewicz, e-mail: olga.grelewicz@gmail.com

Abstract:

Introduction: Prader-Willi Syndrome (PWS) is a genetic disorder marked by hyperphagia, obesity, developmental delays, and behavioral challenges. Traditional treatments like dietary control and growth hormone therapy often fail to effectively manage these symptoms. Recently, glucagon-like peptide-1 (GLP-1) analogs have shown potential in treating PWS. This review assesses the efficacy, safety and mechanisms of GLP-1 analogs in PWS treatment. They improve glycemic control, cardiovascular health, and appetite regulation, contributing to better weight management and overall health in PWS patients. These analogs enhance insulin secretion, inhibit glucagon release, and slow gastric emptying, helping to reduce postprandial glucose spikes and caloric intake.
Results: Several small-scale studies and case reports have shown mixed results regarding the effectiveness of GLP-1 analogs in reducing BMI and hyperphagia in PWS patients. Although the studies demonstrated varied outcomes in terms of BMI reduction, all of them reported

improvement in satiety or appetite levels. **Conclusions**: Overall, GLP-1 analogs hold promise for addressing hyperphagia, obesity, and glycemic control in PWS patients, improving their overall health and quality of life. Continued research and long-term studies are essential to establish these benefits and optimize treatment strategies.

Keywords: Prader Willi Syndrome; obesity; hyperphagia; GLP agonist; GLP-1RA

Introduction

Traditional interventions in controlling the body mass index (BMI) in patients with PWS include dietary control, behavioral therapy, and growth hormone treatment. However, these measures often fall short of effectively managing hyperphagia and obesity. In recent years, glucagon-like peptide-1 (GLP-1) analogs have emerged as a potential therapeutic option for addressing these issues in PWS. This review explores the efficacy, safety, and potential mechanisms of GLP-1 analogs in the treatment of PWS.

State of knowledge:

Prader-Willi Syndrome

Prader-Willi Syndrome (PWS) is a genetic disease that occurs as the result of absence of expression of paternal genes from chromosome 15q11.2-q13 complex disorder affecting multiple systems. Its estimated prevalence ranges from 1 in 10,000 to 1 in 30,000 across various studied populations. PWS presents in early infancy with severe hypotonia with poor suck and feeding difficulties in early infancy. As affected children grow, they typically develop an excessive appetite, leading to morbid obesity unless their food intake is carefully regulated. Developmental delays in motor skills and language, along with some level of

cognitive impairment, are common among individuals with PWS. Both males and females with PWS often experience hypogonadism, characterized by underdeveloped genitalia, incomplete pubertal development, and usually infertility. Short stature is frequently observed and is linked to growth hormone (GH) deficiency. Other common features include distinctive facial characteristics, strabismus, scoliosis, sleep disturbances, and an increased risk of type II diabetes mellitus, particularly in those who are obese. The syndrome is also associated with a distinct behavioral profile, including temper tantrums, stubbornness, and manipulative and compulsive behaviors [1,2].

Hyperphagia and obesity

The prevalence of overweight and obesity in children and adolescents with Prader-Willi syndrome (PWS) is approximately 40% [3]. This percentage increases significantly in adulthood, reaching between 80% and 90% [4,5]. Although the precise mechanism is not yet fully understood, obesity in PWS is primarily linked to dysfunctions in the hypothalamic feeding center and its related hormones, which lead to uncontrolled food intake and disrupted energy expenditure [6].The disruption of the hypothalamic satiety control pathway results in a persistent, unsatisfied appetite, hyperphagia, and eating behaviors. These issues are closely associated with hormonal and neuronal abnormalities that can alter body composition and stimulate excessive eating [7]. Next, an increase in ghrelin has been seen in PWS individuals since they were 5 weeks old [8]. Ghrelin is an orexigenic hormone, an appetite stimulant hormone. The stomach secretes ghrelin during fasting or when hungry. However, the ghrelin level will remain high even after food consumption in PWS. Low peptide YY (PYY) and insulin levels are also involved in hyperphagia and obesity of PWS. The function of PYY and insulin are to stimulate pro-opiomelanocortin (POMC) neurons and inhibit neuropeptide Y (NPY) followed by activation of melanocortin receptor 4 (MC4R) to induce satiety [6]. As PWS individuals have low levels of PYY and insulin, NPY is released and prevents MC4R activation that leads to increased food intake [9,10]. This causes failure of satiety control [7]. Prader-Willi syndrome has traditionally been characterized by two clinical stages: an initial phase of failure to thrive followed by a phase of hyperphagia leading to obesity. However, more recent classification schemes, based on natural history studies, have identified five main nutritional phases that reflect the gradual and complex progression of the disorder:

Phase 0: Occurs in utero, marked by reduced fetal movement and growth restriction.

Phase 1: Infants are hypotonic and not obese (birth to 15 months of age).

- Subphase 1a: Difficulty feeding, potentially accompanied by failure to thrive.
- Subphase 1b: Steady growth and weight gain following a typical growth curve.

Phase 2: Weight gain begins around the age of 2 years.

- Subphase 2a: Weight increases without a corresponding increase in appetite or caloric intake.
- Subphase 2b: Weight gain occurs alongside an increased interest in food.

Phase 3: Characterized by hyperphagia, a lack of satiety, and food-seeking behaviors, typically starting around 8 years of age.

Phase 4: The appetite becomes less insatiable.

Weight management is critical in the care of patients with Prader-Willi syndrome (PWS). A comprehensive survey reported an average age of death of 29.5 years, with obesity identified as a leading cause, accounting for 7% of the mortality rate [11].

Incretins and Glucagon-like peptide-1 receptor agonists (GLP-1RAs) - mechanism of action

Incretins are polypeptide hormones that are secreted by enteroendocrine cells in the mucosal lining of the gut after food intake. They play a crucial role in stimulating insulin release and reducing blood sugar levels after meals. The main incretins are GLP-1, produced by L cells, and GIP, produced by K cells [12]. Because of their short duration of action, these natural hormones are not ideal for therapeutic purposes. However, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been developed as innovative drugs, particularly beneficial for individuals with type 2 diabetes [13,14]. These GLP-1RAs have an extended half-life, allowing for better blood sugar management and significant weight loss. The effectiveness of GLP-1RAs in promoting weight loss is dose-dependent, though their maximum dosage is often constrained by gastrointestinal side effects [12]. Importantly, high-dose versions of GLP-1RAs like liraglutide and semaglutide have been approved not only for managing blood sugar levels but also for treating obesity [15,16].

The potential use of GLP-1 analogs in treating Prader-Willi Syndrome (PWS) hinges on their effectiveness in reducing excessive eating (hyperphagia) and promoting weight loss, targeting two primary symptoms of the disorder. GLP-1 receptor agonists (GLP-1RAs) help control blood sugar levels through various mechanisms: they enhance insulin secretion in response to high blood sugar, suppress glucagon release during hyperglycemia, slow down gastric emptying, prevent large increases in post-meal glucose levels, and lower calorie intake and body weight [17,18,19,20]. Short-acting GLP-1RAs, like lixisenatide, are effective at reducing nighttime and fasting glucose levels while continuing to affect gastric emptying over long-term use. Long-acting GLP-1RAs, such as liraglutide, exenatide, and dulaglutide, exert more significant effects on nighttime and fasting glucose levels and glycated hemoglobin (HbA1c), whether used alone with oral hypoglycemic medications or combined with basal insulin. In obese patients with type 2 diabetes, GLP-1RAs have been demonstrated to significantly reduce body weight [21,22].

Aim

This review aims to discuss the potential use of GLP-1 analogs for weight management in adolescents with obesity due to Prader Willi Syndrome.

Material and methods

Databases such as Pubmed, Medline and Google Scholar were used for research with The key words included: ‘Prader–Willi syndrome ’AND ‘(GLP-1 receptor agonists OR GLP-1 analogues OR incretin mimetics) ’(including all drugs within this subgroup) AND ‘(weight control OR glycaemic control OR appetite regulation)’. Studies that were included in the systematic review are those that evaluated the effects of GLP1-RA in PWS patients of all ages. Several small-scale studies and case reports have explored the use of GLP-1 analogs in patients with PWS.

Results

The latest 52-week, randomized, placebo-controlled, metaanalysis by Diene et al., that included male or female adolescents aged ≥12 to <18 years with pubertal development Tanner

stage 2-5 and children aged ≥6 to <12 years with Tanner stage <2 with obesity >30 BMI and without any type of diabetes showed that BMI decreased from baseline in both children and adolescents; however, there was no significant difference between the liraglutide and placebo groups at week 16, nor between the liraglutide and no treatment groups at week 52. Similarly, for other weight-related endpoints, no significant differences were observed between the liraglutide and placebo/no treatment groups at either 16 or 52 weeks, aligning with the coprimary endpoint findings. However, there was a notable improvement in hyperphagia (total score and drive score) observed in adolescents, which is a critical feature of PWS [23]. In contrast, randomized, double-blind trial, which consisted of a 56-week treatment period and a 26-week follow-up period, that enrolled adolescents (12 to <18 years of age) with obesity showed a reduction in BMI of at least 5% in 51 out of 113 participants in the liraglutide group and in 20 out of 105 participants in the placebo group (estimated percentages of 43.3% vs. 18.7%). Additionally, a reduction in BMI of at least 10% was observed in 33 participants in the liraglutide group and 9 participants in the placebo group (estimated percentages of 26.1% vs. 8.1%) [24].

In another study, exenatide treatment did not lead to significant changes in mean weight, BMI, or BMI z-score over time. However, total appetite scores significantly decreased from baseline after 1, 3, and 6 months of treatment. This reduction was mainly due to decreases in behavior and drive sub-scores, as there was no significant change in the severity score [25]. In the study by Fintini et al., 6 adults with PWS treated with GLP-1 agonists/analogs during the 24 months of treatment had a tendency to decrease BMI, and waist circumference that was more evident during the first 12 months of therapy [26]. A case by Sana et al., reported a patient who after starting exenatide, lost weight continuously until October 2014, reducing weight from 159 kg to 113 kg. Due to poor compliance with the twice-daily dosage, he switched to liraglutide (1.2 mg/day). By July 2022, under regular follow-up and an 1800-calorie diet, his weight was 106,5 kg, totaling a 56,5 kg loss since September 2012 [27]. Another case report also proved that GLP-1 might be helpful in weight loss in patients with PWS. Kim et al., described a 18-years old woman that after liraglutide intake reduced her body weight from 118.6 kg to 104 kg (body mass index [BMI], 50.8 kg/m2) [28].

Discussion

Over time, patient care for PWS has significantly improved, reducing mortality rates and enhancing overall quality of life [29]. This progress is due to a comprehensive, evidence-based approach to managing PWS complications and the standard use of growth hormone therapy from early childhood. However, managing hyperphagia and weight remains challenging [30]. Current obesity management in PWS relies heavily on behavioral strategies, including strict dietary restrictions and supervision, which are demanding for both caregivers and patients due to the inherent food-seeking behaviors, anxiety, compulsive traits, and learning difficulties in PWS. With increased life expectancy, metabolic complications are expected to rise in PWS patients, underscoring the urgent need for better pharmacotherapies to support lifestyle management of hyperphagia and obesity [31].

This review indicates that GLP1-RA is safe for patients with PWS and may offer benefits for weight, glycemic, and appetite control. The reason liraglutide does not reduce BMI SDS in all patients is not fully understood, but it may be linked to the hypothalamic dysregulation characteristic of PWS, which could interfere with liraglutide's effect on appetite centers in the hypothalamus [32,33]. However, it is important to note that GLP-1 receptor agonists have been effective in some patients with hypothalamic obesity due to hypothalamic damage, such as those with craniopharyngioma. This suggests that GLP-1-induced weight loss might not require a fully functional hypothalamus. A case series reported significant weight loss in eight patients with hypothalamic obesity from tumors who were treated with a GLP-1 receptor agonist (exenatide or liraglutide) [34]. Hyperphagia seemed to reduce in adolescents treated with liraglutide, indicating that liraglutide could have had some effect on appetite.

A comprehensive grasp of the pathophysiology of impaired appetite regulation in PWS would represent a crucial advancement, providing valuable insights to steer therapeutic approaches in this domain. Currently, the mechanisms underlying hyperphagia in PWS are not fully elucidated, although they are thought to involve hypothalamic dysfunction, inadequate satiety responses, and dysregulation of appetite-regulating hormones [34,35]. High levels of the orexigenic hormone ghrelin are well-documented in patients with PWS and are widely recognized as crucial in the pathophysiology of hyperphagia. Hyperghrelinemia leads to increased hunger independent of insulin levels in PWS patients.Recent evidence suggests that the ratio of acylated ghrelin to unacylated ghrelin may be more relevant to the

pathophysiology of hyperphagia in PWS than total circulating ghrelin levels [30]. Although endogenous GLP-1 has not been extensively studied in PWS, the limited evidence available does not suggest GLP-1 as a direct cause of hyperphagia. However, animal studies have shown that exendin-4, a GLP-1 receptor agonist, can reduce ghrelin levels, which might be useful in managing hyperghrelinemia-induced hyperphagia [31]. Our systematic review indicates that hyperphagia seemed to reduce in adolescents treated with GLP-1-RA, indicating that they could have had some effect on appetite. Exenatide and liraglutide are the only GLP1-RAs used in PWS patients, both administered via subcutaneous injections. The limited data specific to the PWS population suggest that GLP1-RAs may offer potential benefits for weight and glycemic control, although the exact extent of these benefits is difficult to determine. Additionally, drawing definitive conclusions is challenging because many studies also included other antidiabetic medications and lifestyle interventions. Consistent with the proposed mechanism of appetite suppression by GLP1-RAs, our systematic review indicates that both liraglutide and exenatide resulted in reduced appetite and improved satiety in all assessed patients.

Current limited data suggest that GLP1-RAs may be a promising short-term strategy for weight, glycemic, and appetite control in PWS patients, with no major adverse effects. By reducing weight and improving metabolic profiles. GLP-1 analogs may also contribute to better overall health and quality of life for PWS patients. These findings pave the way for future clinical trials of GLP1-RA in PWS patients, highlighting the need for effective appetite control strategies.

Safety and Tolerability

The safety profile of GLP-1 analogs in PWS appears to be consistent with their use in other populations [38]. Common side effects include gastrointestinal symptoms such as nausea, vomiting, and diarrhea, which are generally transient. Hypoglycemia is rare, given the glucose-dependent mechanism of insulin release. The risk of pancreatitis was previously associated with GLP1-RAs but fortunately not observed in the limited cases we described. However, specific concerns in the PWS population necessitate careful monitoring. The theoretical risk of delayed gastric emptying leading to gastric rupture is significant due to the

high pain threshold and hyperphagia in PWS patients [38,39]. Clinicians should be vigilant for signs of gastrointestinal distress and manage any adverse effects promptly. The exclusion of patients with a history of gastroparesis in trials underscores the need for caution in this area.

Potential Benefits Beyond Weight Management

GLP-1 receptor agonists provide numerous benefits beyond weight management for patients with Prader-Willi Syndrome. They enhance glycemic control by increasing insulin secretion in response to hyperglycemia, inhibiting glucagon secretion. This improved glycemic control is crucial for preventing diabetes and its complications in PWS patients [40].

Additionally, GLP-1RAs offer cardiovascular benefits, including lowering blood pressure, reducing LDL cholesterol levels, and improving endothelial function, thereby reducing the risk of cardiovascular diseases [41].

The appetite-regulating effects of GLP-1RAs can reduce the anxiety and stress associated with constant hunger and food-seeking behavior in PWS patients, leading to an improved quality of life, better social interactions, and enhanced mental health and well-being.

Furthermore, GLP-1RAs may contribute to better bone density and skeletal health, indirectly supporting weight-bearing activities and potentially influencing bone metabolism, thus mitigating the risks of osteoporosis and fractures common in PWS patients [42].

Emerging evidence suggests that GLP-1RAs may have neuroprotective properties, supporting cognitive function and protecting against neurodegenerative processes, which can be beneficial for PWS patients with cognitive impairments although this remains speculative and warrants further investigation [43].

Overall, the use of GLP-1 analogs in patients with Prader-Willi Syndrome offers a multifaceted approach that addresses several key aspects of health, improving overall patient outcomes beyond weight management.

Conclusion

The use of GLP-1 analogs in the weight management of patients with Prader-Willi Syndrome (PWS) represents a promising advancement in addressing the complex and multifaceted challenges posed by this condition. Managing obesity in PWS is particularly challenging due

to the insatiable hunger and compulsive eating behaviors associated with the syndrome. While early studies and case reports provide encouraging results, there is a pressing need for larger, well-designed clinical trials to robustly assess their efficacy and safety in this unique patient population. Additionally, long-term studies are necessary to understand the potential impacts on growth, pubertal development, and overall metabolic health in individuals with PWS. As research progresses, GLP-1 analogs may become a cornerstone in the multidisciplinary management of PWS, improving the quality of life and health outcomes for affected individuals.

The integration of GLP-1 analogs into the management of PWS could represent a paradigm shift in treating this challenging condition. By providing an effective pharmacological option to complement dietary and behavioral interventions, GLP-1 analogs offer a comprehensive approach to managing obesity in PWS. This could alleviate some of the burdens on patients and caregivers, making weight management more feasible and less stressful.

Authors Contribution:

Conceptualization: Olga Grelewicz, Adam Juśkiewicz;
methodology: Elwira Servaas;
software: Mateusz Haber;
check: Natalia Kucy, Paula Kula, Adrianna Czachor;
formal analysis: Alicja Kotula;
investigation: Elwira Servaas;
resources: Paula Kula;
data curation: Natalia Kucy;
writing - rough preparation: Olga Grelewicz;
writing - review and editing: Adam Juśkiewicz;
visualization: Mateusz Haber;
supervision: Alicja Kotula;
project administration: Olga Grelewicz.
All authors have read and agreed with the published version of the manuscript

Conflict of interest: The authors declare no conflict of interest.

Funding:This review has not received any external funding.

Statement of institutional review committee: not applicable

Informed consent: not applicable

Data availability: not applicable

Acknowledgments: not applicable

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