

REVISIÓN: A PROPÓSITO DE UN CASO

Effect of semaglutide on weight loss and glycaemic control in patients with Prader–Willi Syndrome and type 2 diabetes



Olga Giménez-Palop^{a,b,*}, Ana Romero^a, Laia Casamitjana^{a,b}, Rocio Pareja^{a,b}, Mercedes Rigla^{a,b}, Assumpta Caixàs^{a,b}

^a Endocrinology and Nutrition Department, Hospital Universitari Parc Taulí, Corporació Sanitària Parc Taulí, Universitat Autònoma de Barcelona, Sabadell, Spain

^b Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain

Received 23 June 2023; accepted 28 December 2023

Available online 9 February 2024

KEYWORDS

Prader–Willi Syndrome;
Diabetes mellitus;
Semaglutide;
Obesity

Abstract Prader–Willi Syndrome (PWS) is the most common genetic cause of obesity, occurring in approximately 1 in 15,000 newborns. It results from the lack of expression of genes on the paternal allele of the chromosomal region 15q-11q13 (65–75% due to type 1 or type 2 deletion). Individuals with PWS experience associated symptoms such as hypotonia, hyperphagia, and early-onset obesity (before 5 years of age). Around 20% of adults with PWS also develop type 2 diabetes. Previous studies have shown the beneficial effects of GLP1-RA medications, such as exenatide and liraglutide, in treating type 2 diabetes in PWS. However, there is limited information available on the use of semaglutide in PWS. This study aimed to evaluate the effects of semaglutide on weight loss and glycaemic control in four patients with PWS and type 2 diabetes associated with obesity. The patients were started on weekly subcutaneous progressive doses of semaglutide.

© 2024 SEEN y SED. Published by Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE

Síndrome de Prader–Willi;
Diabetes mellitus;
Semaglutida;
Obesidad

Efecto de la semaglutida sobre la pérdida de peso y el control glucémico en pacientes con síndrome de Prader–Willi y diabetes tipo 2

Resumen El síndrome de Prader–Willi (SPW) es la causa más común de obesidad genética, con una incidencia de 1:15.000 recién nacidos. Se produce por una falta de expresión de los genes ubicados en el alelo paterno de la región cromosómica 15q-11q13 (65-75%) debido a la delección tipo 1 o tipo 2. Presentan hipotonía, hiperfagia y obesidad de inicio temprano (antes de los 5 años de edad). Hasta el 20% de los pacientes en la edad adulta tienen diabetes tipo 2. Se

* Corresponding author.

E-mail addresses: olga.gimenez@yahoo.com, ogimenez@tauli.cat (O. Giménez-Palop).

han descrito efectos beneficiosos de GLP1-RA, exenatida y liraglutida en el tratamiento de la diabetes tipo 2 en este síndrome.

Actualmente hay poca información sobre el uso de semaglutida en el SPW. El objetivo fue evaluar el efecto de semaglutida en la pérdida de peso y el control glucémico en una serie de 4 pacientes con SPW y diabetes tipo 2 asociada a obesidad que comenzaron con semaglutida subcutánea semanal en dosis progresivas.

© 2024 SEEN y SED. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Prader-Willi Syndrome (PWS) is the most prevalent cause of syndromic obesity, estimated to affect 1 in 10,000 to 1 in 30,000 newborns. It arises due to the absence of gene expression from the paternal origin within the 15q11-q13 chromosomal region. Approximately 65–75% of cases result from a deletion (type I and type II), while maternal uniparental disomy accounts for 20–30%, and an imprinting defect account for 1–3%.¹ PWS is characterized by persistent neonatal hypotonia, short stature due to growth hormone deficiency, hypogonadism, varying degrees of intellectual disability, and hyperphagia starting in early childhood (before the age of 5), leading to severe obesity.^{2–4} Obesity is the primary cause of increased morbidity and mortality in individuals with this syndrome. Diabetes typically manifests in 10–25% of PWS patients, typically during adulthood. Paradoxically, despite severe obesity, relative hypoinsulinemia is frequently observed.⁵

The exact pathophysiology of obesity in PWS is not fully understood but is likely the result of a combination of hypothalamic dysfunction leading to hyperphagia, dysregulation of hormones controlling hunger and satiety, reduced baseline energy expenditure, and deficiencies in various hormones (e.g., growth hormone, hypogonadism, hypothyroidism).

Obesity affects approximately 40% of children and adolescents with PWS and increases to over 90% in adulthood.^{6–8}

Previous studies have shown the beneficial effects of an analogue of glucagon-like peptide-1 (GLP1-RA) medications, such as exenatide and liraglutide, in treating type 2 diabetes in PWS. However, there is limited information available on the use of semaglutide in PWS. This study aimed to evaluate the effects of semaglutide on weight loss and glycaemic control in four patients with PWS and type 2 diabetes associated with obesity.

Description of cases and management

Table 1 summarizes the characteristics of the patients.

Written informed consent was obtained from all patients and/or parents or legal representatives.

Case 1: A 40-year-old man with PWS, resulting from a type II deletion, visited our Specialized Unit. His medical history included hypogonadism, asthma, obstructive sleep apnoea syndrome (treated with CPAP), and scoliosis. He initiated growth hormone (GH) five years ago (0.8 mg per week), hav-

ing not received GH during childhood. He developed type 2 diabetes at the age of 35 without any chronic complications. His diabetes treatment consisted of glargine insulin (22 units twice daily), empagliflozin (10 mg daily), and metformin (850 mg twice daily). At the beginning of the study, his weight was 95.5 kg, height 143 cm, BMI 46.7 kg/m², and glycated haemoglobin was 9%. The Endocrinologist added subcutaneous semaglutide 0.25 mg per week to his treatment, which was later increased to 0.5 mg per week after a month. After six months of treatment with semaglutide 0.5 mg per week, he achieved a weight loss of 5 kg and improved glycaemic control with a glycated haemoglobin of 7%. This improvement was maintained one year later. Subsequently, he was advised to increase the dose to 1 mg, but he was unable to start due to lack of supply. As a result, he switched to liraglutide at a dose of 1.8 mg daily, which led to weight gain and worsening of glycaemic control.

Case 2: A 43-year-old woman with PWS, resulting from a type I deletion, visited our Specialized Unit. Her medical history included hypogonadism, obstructive sleep apnoea syndrome (treated with CPAP), scoliosis, and bacterial endocarditis requiring surgical intervention. Similar to Case 1, she did not receive GH treatment during childhood but started GH at adult doses five years ago (1.4 mg per week). She developed type 2 diabetes at the age of 33 without any chronic complications, and her glycated haemoglobin was relatively well controlled at 7.4%. At the start of the study, she was being treated with metformin (850 mg twice daily), empagliflozin (10 mg daily), and glargine insulin (6 units at bedtime). Her weight was 63.5 kg, height 143 cm, and BMI 31 kg/m². Semaglutide 0.25 mg per week was added to her treatment, this dose was well tolerated, so she increased the dose to 0.5 mg per week and finally to 1 mg per week. She improved glycaemic control, stopped insulin and achieved a glycated haemoglobin of 6.5% and lost weight up to 48.5 kg after 6 months with the last dose change, 24 months after the beginning of semaglutide. However, she regained weight up to 52 kg at 36 months with the same glycated haemoglobin.

Case 3: A 31-year-old woman with PWS, resulting from a type I deletion, visited our Specialized Unit. She did not receive GH treatment during childhood but started GH at adult doses 5 years ago (2.8 mg per week). She had type 2 diabetes with suboptimal control (glycated haemoglobin of 7.5%) under treatment with metformin 850 mg twice daily and empagliflozin 10 mg a day. Before starting with semaglutide, her weight was 84.5 kg (BMI: 41.9 kg/m²). The initial

Table 1 Characteristics of patients.

Case	(M/F) years	Weight (kg)	BMI (kg/m ²)	HbA1c (%)	Treatment for DM2	Semaglutide dose (mg/week)/time	Weight (kg) evolution	HbA1 (%) evolution
1	M 40	95.5	46.7	9	Metformin 850 mg twice daily Empagliflozin 10 mg a day Glargine 22-0-22 UI	0.5 mg 18 months	90.5	7
2	F 43	63.5	31	7.4	Metformin 850 mg twice daily Empagliflozin 10 mg a day Glargine 6-0-0	1 mg 36 months	52	6.5
3	F 31	84.5	41.9	7.5	Metformin 850 mg twice daily Empagliflozin 10 mg a day	1 mg 36 months	84.3	7.7
4	M 25	101	32.9	7.2	Metformin 1000 mg twice daily Empagliflozin 25 mg a day Glargine 32-0-0 UI	0.5 mg 12 months	105.9	6.7

Abbreviations: BMI, body mass index; HbA1c, glycosylated haemoglobin; DM2, type 2 diabetes mellitus.

dose of semaglutide was 0.25 mg subcutaneously per week and one month later increased to 0.5 mg per week. After 12 months she lost 2 kg and her glycated haemoglobin was 6.9%. Later on, she increased her weight 2 kg so the physician increased semaglutide dose to 1 mg per week but maintained the same weight and the glycaemic control deteriorated reaching again a glycated haemoglobin of 7.7%.

Case 4: A 25 years old man with PWS due to a deletion type II was visited in our Specialized Unit. He had not received GH treatment during childhood. He started GH treatment 3 years ago at adult doses 1.4 mg per week. He had type 2 diabetes and obesity (weight 101 kg, height 175, BMI: 32.97 kg/m²). His treatment was: glargine insulin 32 UI before breakfast, metformin 1000 mg twice daily and empagliflozin 25 mg a day. His glycated haemoglobin was 7.2%. After 6 months with semaglutide 0.25 mg a day, his weight and glycaemic control did not change. His physician encouraged him to increase semaglutide dose but he refused and stopped the treatment. Later on, he resumed treatment with semaglutide and increased the dose to 0.5 mg per week. After 6 months with this dose, his glycated haemoglobin dropped from 7.4% to 6.7% and his weight increased from 101.5 kg to 105.9 kg.

Discussion

In this investigation, we assessed the impacts of semaglutide, an analogue of glucagon-like peptide-1 (GLP1-RA), on the reduction of weight and regulation of blood sugar levels in four adult patients diagnosed with Prader–Willi Syndrome (PWS) and type 2 diabetes. In all patients, semaglutide once a week was well tolerated. The first two patients

(cases 1 and 2) experimented an improvement of weight and glycaemic control. Case 3 experimented an initial improvement in weight and glycaemic control but with later regain of weight and a deterioration of glycated haemoglobin. Finally, case 4 experimented an improvement in glycaemic control but with weight gain.

Numerous clinical trials have been conducted to date, using different medications aiming to reduce hunger in these patients, but without success.⁹

GLP1-RA are increasingly being employed to treat obesity in patients with or without type 2 diabetes. Glucagon-like peptide is a gut hormone produced by L-cells in response to food intake.¹⁰ Its functions include stimulating insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety after meals. Impaired secretion and action of GLP-1 have been implicated in the pathophysiology of obesity and type 2 diabetes. Exenatide, approved by the US Food and Drug Administration (FDA) in 2005, was the first aGLP-1 medication used to treat type 2 diabetes.¹¹ More recently, liraglutide has been approved by the FDA and the European Medicines Agency (EMA) for obesity treatment (without diabetes) in adults and adolescents.^{12,13}

GLP1-RA has been used with some success in patients with hypothalamic obesity,^{14,15} making it a potentially viable option for individuals with PWS. Liraglutide specifically acts on the pro-opiomelanocortin and cocaine-amphetamine-regulated transcript (POMC/CART) neurons within the arcuate nucleus, the primary centre regulating appetite in the hypothalamus.¹⁶ Furthermore, studies have shown that liraglutide reduces levels of ghrelin, an appetite-stimulating peptide that is elevated in PWS during fasting and after meals.¹⁷

The results of the main studies carried out in patients with PWS with GLP1-RA are summarized below. Some explored the effect on weight and appetite in obese PWS patients without diabetes mellitus^{18,19} and others also explored the effect on glycaemic control.^{20,21}

Diene et al.¹⁸ studied the effect of GLP1-RA on weight with liraglutide treatment compared with placebo in paediatric individuals (31 adolescents and 24 children) with PWS and obesity in a multicentre, 52-week, placebo-controlled trial with poor results. The change in BMI standard deviation score from baseline to weeks 16 and 52 did not differ significantly between the treatment and placebo groups in both adolescents (estimated treatment difference: -0.07 at week 16 and -0.14 at week 52) and children (-0.06 and -0.07 , respectively). However, at week 52, treated adolescents exhibited lower hyperphagia total and drive scores compared to the no-treatment group. The most common adverse events associated with liraglutide treatment were gastrointestinal disorders.

Goldman et al.¹⁹ reported a series of cases and conducted a literature review on the use of anti-obesity medications (AOMs) in children and adolescents with PWS and obesity. The case series included PWS patients with obesity but without diabetes who were treated with metformin, topiramate, liraglutide, and semaglutide. The cases demonstrated that patients with PWS and obesity can benefit from various AOMs with minimal adverse effects and varying degrees of weight reduction. Two 12-year-old males in the series were treated with subcutaneous semaglutide 1 mg per week for 16 weeks as part of combination therapy (including metformin + topiramate). One patient experienced an increase in zBMI ($+0.02$) and weight ($+2.4$ kg) at the fourth month compared to baseline, while the other patient showed a decrease in zBMI (-0.02) and weight (-5.7 kg) during the same period.

The literature review conducted by Goldman et al.¹⁹ included studies involving PWS patients with obesity (some with diabetes) who were treated with topiramate, metformin, phentermine, orlistat, liraglutide, oxytocin, naltrexone-bupropion, or various combinations of these medications. The review revealed improvements in hyperphagia and social behaviour, but the effects on BMI or weight loss were variable and limited. Liraglutide, often used in combination with other anti-obesity medications like metformin or empagliflozin, demonstrated the most promising effects on weight loss. The studies on liraglutide often reported decreases in HbA1c (ranging from -1.3% to -1.9% over 14–16 weeks or no decrease) and variable effects on weight (ranging from -3.2 kg to no change) without significant side effects.

Beng et al. conducted a systematic review examining the impact of aGLP1 (exenatide and liraglutide) on weight loss and glycaemic control in Prader-Willi Syndrome.²⁰ The review included ten studies, involving a total of 23 PWS patients (aged 13–37 years) who were treated with either exenatide ($n=14$) or liraglutide ($n=9$) for durations ranging from 14 weeks to 4 years. Of these patients, 16 (70%) had type 2 diabetes. Ten patients experienced improvements in body mass index (BMI), ranging from 1.5 to 16.0 kg/m², while 19 of the 23 cases showed improvements in HbA1c levels, ranging from 0.3% to 7.5%. Appetite and satiety levels were

reported to improve in all five studies. No serious side effects were reported.

Finally, Sani et al.²¹ reported a case of a 33-year-old man with Prader-Willi Syndrome complicated by poorly controlled diabetes and severe obesity. This individual was treated with subcutaneous semaglutide 1 mg per week. After 12 months of treatment, significant reductions in glycated haemoglobin levels (from 11.1% to 7.2%) and body weight (from 99.5 kg to 94.3 kg) were observed, along with a notable decrease in fat mass and insulin requirements. It is worth noting that this patient had previously tried liraglutide therapy in combination with metformin and insulin without significant efficacy.

As in our series, the results in terms of weight loss and improvement in glycaemic control were heterogeneous in those patients treated with GLP1-AR. This circumstance can also be observed in routine clinical practice in patients with obesity and type 2 diabetes mellitus without PWS in terms of glycaemic control. Current evidence on treatment effect heterogeneity for this therapy is limited, possibly reflecting the methodological limitations of published studies so far.²²

In summary, the use of GLP1-RA medications, such as liraglutide and semaglutide, has shown some promising effects in the treatment of obesity and glycaemic control in individuals with PWS. These medications have demonstrated improvements in BMI, HbA1c levels, and satiety levels in some individuals. However, it is important to note that the long-term effects and efficacy of GLP1-RA in PWS are still uncertain and robust and appropriately powered studies are required to understand treatment effect heterogeneity and evaluate the potential for precision medicine to provide future clinical care.

Areas of uncertainty

Taking into account this series of cases and the literature review, it can be deduced that managing diabetes and obesity in individuals with Prader-Willi Syndrome (PWS) is challenging due to the inherent food behaviour associated with hyperphagia. The long-term effects of GLP1-RA in PWS remain uncertain, and further studies are needed.

Conclusion

The treatment of hyperphagia in PWS remains a challenge. Semaglutide, administered once weekly, can be effective and safe for some patients with PWS and type 2 diabetes mellitus associated with obesity.

Guidelines and recommendations

While there is no specific treatment for diabetes and obesity in PWS, we encourage the use of medications that have a favourable effect on weight loss, despite the possibility of short-lived effects.

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

During the preparation of this work the author(s) used ChatGPT in order to Improve language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Funding

No grants supported the writing of this manuscript.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank the patients and their families.

References

- Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader–Willi Syndrome. *Genet Med Off J Am Coll Med Genet*. 2012;14:10–26.
- Butler MG, Miller JL, Forster JL. Prader–Willi Syndrome – clinical genetics diagnosis and treatment approaches: an update. *Curr Pediatr Rev*. 2019;15:207–44.
- Moix E, Giménez-Palop O, Caixàs A. Treatment with growth hormone in the Prader–Willi Syndrome. *Endocrinol Diabetes Nutr (Engl Ed)*. 2018;65:229–36.
- Guinovart M, Coronas R, Caixàs A. Psychopathological disorders in Prader–Willi Syndrome. *Endocrinol Diabetes Nutr (Engl Ed)*. 2019;66:579–87.
- Crinò A, Grugni G. Update on diabetes mellitus and glucose metabolism alterations in Prader–Willi syndrome. *Curr Diab Rep*. 2020;20:7.
- Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, et al. Endocrine disorders in children with Prader–Willi Syndrome – data from 142 children of the French database. *Horm Res Paediatr*. 2010;74:121–8.
- Grugni G, Crinò A, Bosio L, Corrias A, Cuttini M, De Toni T, et al. The Italian National Survey for Prader–Willi Syndrome: an epidemiologic study. *Am J Med Genet A*. 2008;146A:861–72.
- Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HMJ, van Nieuwpoort IC, Drent ML, Curfs LMG, et al. Physical health problems in adults with Prader–Willi Syndrome. *Am J Med Genet A*. 2011;155A:2112–24.
- Tan Q, Orsso CE, Deehan EC, Triador L, Field CJ, Tun HM, et al. Current and emerging therapies for managing hyperphagia and obesity in Prader–Willi Syndrome: a narrative review. *Obes Rev Off J Int Assoc Study Obes*. 2020;21:e12992.
- Anandhakrishnan A, Korbonits M. Glucagon-like peptide 1 in the pathophysiology and pharmacotherapy of clinical obesity. *World J Diabetes*. 2016;7:572–98.
- Barnett A. Exenatide. *Expert Opin Pharmacother*. 2007;8:2593–608.
- Nordisk N. FDA approves Saxenda for the treatment of obesity in adolescents aged 12–17; 2020. <https://www.novonordisk-us.com/media/news-releases.html?123001> [accessed 10.6.21].
- Nordisk N. EMA approves liraglutide for teenagers with obesity. <https://diabetes.medicinematters.com/liraglutide-obesity-/adolescents/>.
- Zoicas F, Droste M, Mayr B, Buchfelder M, Schöfl C. GLP-1 analogues as a new treatment option for hypothalamic obesity in adults: report of nine cases. *Eur J Endocrinol*. 2013;168:699–706.
- Roth CL, Perez FA, Whitlock KB, Elfers C, Yanovski JA, Shoemaker AH, et al. A phase 3 randomized clinical trial using a once-weekly glucagon-like peptide-1 receptor agonist in adolescents and young adults with hypothalamic obesity. *Diabetes Obes Metab*. 2021;23:363–73.
- Secher A, Jelsing J, Baquero AF, Hecksher-Sørensen J, Cowley MA, Dalbøge LS, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124:4473–88.
- Senda M, Ogawa S, Nako K, Okamura M, Sakamoto T, Ito S. The glucagon-like peptide-1 analog liraglutide suppresses ghrelin and controls diabetes in a patient with Prader–Willi Syndrome. *Endocr J*. 2012;59:889–94.
- Diene G, Angulo M, Hale PM, Jepsen CH, Hofman PL, Hokken-Koelega A, et al. Liraglutide for weight management in children and adolescents with Prader–Willi syndrome and obesity. *J Clin Endocrinol Metab*. 2022;108:4–12.
- Goldman VE, Naguib MN, Vidmar AP. Anti-obesity medication use in children and adolescents with Prader–Willi syndrome: case review and literature search. *J Clin Med*. 2021;10:4540.
- Ng NBH, Low YW, Rajgor DD, Low JM, Lim YY, Loke KY, et al. The effects of glucagon-like peptide (GLP)-1 receptor agonists on weight and glycaemic control in Prader–Willi Syndrome: a systematic review. *Clin Endocrinol (Oxf)*. 2022;96:144–54.
- Sani E, Prato GD, Zenti MG, Bordugo A, Trombetta M, Bonora E. Effects of semaglutide on glycemic control and weight loss in a patient with Prader–Willi syndrome: a case report. *Endocr Metab Immune Disord Drug Targets*. 2022;22:1053–7.
- Young KG, Mc Innes EH, Massey RJ, Kahkoska AR, Pilla SJ, Raghavan S, et al. Treatment effect heterogeneity following type 2 diabetes treatment with GLP1-receptor agonists and SGLT-2-inhibitors: a systematic review. *Commun Med (Lond)*. 2023;3:131.