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Efficacy Of GLP-1 Receptor Agonists in the Management of Hyperphagia, Severe Obesity, and Liver Steatosis/Fibrosis Indices in Prader Willi Syndrome: Two Case Reports

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Abstract

Hyperphagia and severe obesity resistant to dietary interventions represent common clinical features of Prader Willi Syndrome (PWS). Currently, there are no drugs approved for the treatment of hyperphagia in PWS patients. Liraglutide and semaglutide are glucagon-like peptide-1 receptor agonist (GLP-1-RA) approved for the treatment of non-syndromic obesity. Here we describe the cases of two young female patients with PWS and without type 2 diabetes, resistant to previous weight loss attempts, who were sequentially treated with liraglutide and semaglutide, associated with a mild hypocaloric diet. Hyperphagia, assessed by Hyperphagia Questionnaire (HQ), quality of life (QoL), assessed by The Short Form-36 (SF-36), anthropometric measurements, metabolic profile, and liver steatosis/fibrosis indices, were evaluated at baseline, after the treatment with liraglutide, and after subsequent treatment with semaglutide. In our cases, the sequential treatment with liraglutide and semaglutide, in addition to a mild hypocaloric diet, led to improvements in hyperphagia, excess body weight, insulin resistance, and indices of hepatic steatosis/fibrosis, which were not previously achieved with diet alone. These results support the use of GLP-1 RAs as valid therapeutic strategy for managing hyperphagia and weight loss in patients with PWS.

Keywords: Glucagon Like Peptide-1 receptor agonists; Prader Willi Syndrome; liraglutide, semaglutide, hyperphagia, syndromic obesity.

Introduction

Prader Willi syndrome (PWS) is a rare genetic disease, caused by the loss of expression of the paternal genes of chromosome 15q11-q13, determined by paternal deletion (65-70%), maternal uniparental disomy (20-30%), or imprinting defects (1-3%). PWS, resulting by impaired hypothalamic neurodevelopment, is characterized by severe hypotonia and feeding disorders in the neonatal period, followed by developmental delay and/or intellectual disability, dramatic hyperphagia, and endocrine dysfunctions that lead to progressive, severe obesity throughout adult life. Severe obesity is associated with cardiometabolic risk factors, such as hypertension, dyslipidemia, type 2 diabetes and MAFLD (liver disease associated with metabolic dysfunction) that have a significant impact on the overall mortality of the population affected by PWS [1].

Subjects with PWS have low compliance to follow food restrictions, due to their increased food-seeking behaviour, with inability to comply with the proposed dietary programs [1]. Liraglutide and semaglutide are Glucagon Like Peptide-1 receptor agonists (GLP-1-RA) approved for the treatment of obesity and overweight, that improve glycemic control and increase satiety [2]. A double-blind multicenter study lasting 52 weeks compared liraglutide with placebo in a group of PWS patients aged 6 to 17 years, obtaining no significant changes in body mass index (BMI), despite an improvement in hyperphagia [3]. In contrast, two case reports in PWS patients on treatment with liraglutide showed a significant weight loss after treatment [4,5]. More recently, a case report described the long-term efficacy and safety of semaglutide treatment for obesity in patients with PWS [6]. Therefore, GLP-1-RAs have given only partial and conflicting results, and currently there are no drugs approved for the treatment of hyperphagia in patients with PWS [7]. However, GLP-1-RAs have been indicated as potentially effective for managing hypothalamic obesity [8].

We report the cases of two young female patients with PWS, without type 2 diabetes, admitted to the outpatient obesity clinic of the Endocrinology Unit at Federico II University Hospital, whose hyperphagia, severe obesity, metabolic profile, and liver steatosis/fibrosis indices improved after sequential treatment with liraglutide and semaglutide, associated with a mild hypocaloric diet.

Material and Methods

After obtaining written informed consent from the caregivers, liraglutide was initially administered at a dose of 0.6 mg/day subcutaneously and gradually increased over 4 weeks to the final dose of 3.0 mg/day, in addition to a mild hypocaloric diet without further modifications to lifestyle. As semaglutide has been available in Italy since July 2024 in patients with obesity and without diabetes, and considering the superiority of semaglutide in terms of weight loss [9], both patients were switched from liraglutide to semaglutide. In particular, patient A was switched to semaglutide after 12 months, and patient B after 6 months. Semaglutide was administered at the starting dose of 0.25 mg subcutaneously once a week, and gradually up titrated at weekly intervals until reaching a dosage of 2.4 mg subcutaneously once a week. For safety monitoring, fasting plasma glucose, amylase, and lipase were measured to monitor the potential onset of adverse effects. During liraglutide and subsequent semaglutide treatment, the patients did not report any significant side effects, except for mild-to-moderate and transient nausea occurring during the liraglutide dose-escalation period, which did not require drug discontinuation or dose changes. Hyperphagia, assessed using a validated questionnaire (the 11-item version of the Hyperphagia Questionnaire) [10], with a 5-point scale response (from 1 to 5), and Quality of life (QoL), assessed by The Short Form-36 (SF-36) were administered to the usual caregiver of the patient. Body composition was assessed using bioelectrical impedance analysis (BIA). Metabolic and liver parameters, including the homeostatic model assessment of insulin resistance (HoMA-IR), fatty liver index (FLI), fibrosis 4 (FIB-4) index, Hepatic Steatosis Index (HIS), and the NAFLD fibrosis score, were also evaluated. HoMA-IR was calculated according to Matthews et al. and a value of HoMA-IR > 2.5 was used as cut-off of insulin resistance [11]. FIB-4 index to predict fibrosis was calculated as previously reported [12]. FIB4 allows a classification of individuals based on risk categories for liver fibrosis, namely high risk (FIB-4 ≥ 3.25) and low risk (FIB-4 < 1.3) and it can be considered a valid alternative to liver biopsy for diagnosing liver fibrosis and its management at community level. The Fatty Liver Index (FLI) is used to discriminate between healthy individuals and those with nonalcoholic fatty liver disease (NAFLD) [13]. If the score is >60, we can predict NAFLD. The Hepatic Steatosis Index (HSI) is a useful tool for screening Non-Alcoholic Fatty Liver Disease (NAFLD) [14]. An HSI value >36 is considered indicative of NAFLD, requiring further diagnostic and therapeutic evaluation. The NAFLD fibrosis score (NFS) identifies NAFLD patients with and without advanced fibrosis at initial NAFLD diagnosis [15]. NAFLD patients with a score less than -1.5 were classified as “low probability of advanced liver fibrosis,” and those patients with a score of at least -1.5 were classified as “intermediate or high probability of advanced liver fibrosis”.

Case Series

Case Presentation: Patient A

Patient A is a 28-year-old female, affected by PWS diagnosed at birth through genetic testing which identified the deletion in the

region located in the proximal part of chromosome 15. In July 2023, the patient was admitted to our outpatient obesity clinic for severe obesity (BMI 44 kg/m2), complicated by insulin resistance, metabolic dysfunction-associated fatty liver disease (MAFLD), and obstructive sleep apnea syndrome (OSAS). The patient had a clinical history of primary amenorrhea, but hormone therapy was discontinued early within a year due to a deep vein thrombosis event. The patient was unable to comply with the prescribed dietary program (mild hypocaloric diet: 1400 kcal/day, 55% carbohydrates, 30% fats, and 15% proteins), and was on treatment with calcium carbonate (1000 mg) + vitamin D3 (880 IU) 1 tablet/day; perphenazine 4 mg 2 tablets/day. The diagnosis of liver steatosis/fibrosis was obtained through transient elastography (TE-Fibroscan®). As previously reported [16], the stiffness threshold values were F1 (little or no scarring in the liver) ≤7.5 kPa; F2 (moderate scarring in the liver) 7.5 to 10 kPa; F3 (severe scarring in the liver) 10 to 14 kPa; F4 (very severe scarring in the liver) ≥14 kPa. The Controlled Attenuation Parameter (CAP) was S1 (11%–33% of the liver affected by fatty change): 238–260 dB/m; S2 (34%–66% of the liver affected by fatty change): 260–290 dB/m; S3 (>67% of the liver affected by fatty change): 290–400 dB/m. As reported in Table 1, the hyperphagia score dropped from 16 to 6 after treatment with liraglutide, with a meaningful reduction in food seeking, that further reduced to 4 after 6 months of treatment with semaglutide (Table 1). The patient achieved a weight loss of 26.3 kg, with a percentage weight loss (%WL) and percentage excess weight loss (%EWL) of 28% and 64%, respectively. A reduction in waist circumference of 22 cm and an improvement in lean mass percentage from 48.8% to 65% were also observed. Weight loss was associated with an improvement in insulin resistance, despite comparable fasting plasma glucose levels (Table 2). Table 3 reports also liver steatosis/fibrosis values obtained by Fibroscan and liver indices. Specifically, a significant reduction in liver fibrosis was observed, resulting in a transition from severe (F3) to moderate fibrosis (F2), in association with improvements in FLI, HIS, FIB-4 and NAFLD fibrosis scores. Moreover, there was an increase in quality of life (QoL), with improvements in role limitations due to physical health and emotional problems. The patient was also motivated to start a structured physical activity program.

Case Presentation: Patient B

Patient B is a 34-year-old female, affected by PWS diagnosed at birth through genetic testing which identified the deletion in the region located in the proximal part of chromosome 15.She was admitted in September 2023 to our outpatient obesity clinic for severe obesity (BMI 71 kg/m2), complicated by insulin resistance, and MAFLD. Until then, the patient firmly rejected any nutritional approach, displaying outbursts of anger and highly aggressive behaviours directed at the caregiver and healthcare staff.The patient was on treatment with vitamin D3 (1000 IU) 1 tablet/day, and simvastatin 20 mg 1 tablet/day. During treatment, no significant side effects were reported. After liraglutide treatment the hyperphagia score decreased from 33 to 26, with a further decrease to 16 after 6 months of treatment with semaglutide (Table 1). A weight loss of 60 kg was achieved, with a %WL and %EWL of 38% and 60%, respectively. A reduction in waist circumference of 54 cm and an improvement in lean mass percentage from 38.7% to 57.5% were also observed (Table 2). Similarly, the weight loss was associated with an improvement in insulin resistance, despite comparable fasting plasma glucose levels (Table 3). An increase in QoL was also observed, with improvements in role limitations due to physical health and emotional issues. During the treatment the patient was motivated to start a structured physical activity program. In this case, a FibroScan was not performed. However, a significant improvement in liver indices (FIB-4, FLI, HSI, NAFLD score) was observed, as shown in the table 3.

	Patient A			**Patient B**		
	Baseline	Liraglutide	Semaglutide	Baseline	Liraglutide	Semaglutide
During the past 2 weeks, how upset did the person generally become when denied a desired food?	2	1	1	4	4	3
During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?	1	1	0	3	2	2
During the past 2 weeks, once your person thinks about food, is it easy for you or for other people to divert his attention away from food to other things?	2	1	0	4	3	2
During the past 2 weeks, how often did the person forage through trash for food?	0	0	0	2	2	0
During the past 2 weeks, how often did the person get up at night to food seek?	0	0	0	2	2	2
During the past 2 weeks, how persistent was the person in asking or looking for food after being told “no” or “no more”?	2	0	0	3	2	1
During the past 2 weeks, outside of normal mealtimes, how much time did the person generally spend asking or talking about food?	3	3	1	3	3	1
During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?	2	1	0	3	2	2
During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?	1	0	0	2	1	1
During the past 2 weeks, to what extent can your child be shrewd or quick at getting food?	1	1	1	3	3	1
During the past 2 weeks, how often did food-related behavior interfere with the person’s normal daily activities, such as self-care, recreation, school, or work?	2	1	1	4	2	1
TOTAL	16	6	4	33	26	16

Table 1: 11-items Hyperphagia Questionnaire (HQ) administered to the patient A usual caregivers at baseline, after 12-months treatment with liraglutide and after 6-months treatment with semaglutide. HQ was administered to Patient B usual caregiver at baseline, and after 6-months treatment with liraglutide and after 6-months treatment with semaglutide.

	Patient A				Patient B			
	Baseline	Liraglutide	Semaglutide	Δ	Baseline	Liraglutide	Semaglutide	Δ
Height (cm)	146	-	-	-	147	-	-	-
Weight (kg)	93.7	83.2	67.4	26.3	154	108.3	94	60
BMI (kg/m2)	44	39	31.6	12.3	71	50.1	43.5	27.5
WC (cm)	109	99	87	22	163	120	109	54
FM (kg)	47.9	40.5	23.6	24.3	94.4	51.9	39.9	54.5

FM (%)	51.2	47.9	35	16.2	61.3	48.3	42.5	16.2
LBM (kg)	45.8	42.7	43.8	2	59.6	56.4	54.1	5.5
LBM (%)	48.8	51.4	65	16.2	38.7	51.7	57.5	18.8
Body composition was evaluated by bioelectrical impedance analysis (BIA). WC, waist circumference; FM, Fat Mass; LBM, Lean Body Mass. Patient A was evaluated at baseline, after 12-month treatment with liraglutide, and after 6 months treatment with semaglutide. Patient B was evaluated at baseline, after 6-month treatment with liraglutide and after 6-months treatment with semaglutide.								

Table 2: Anthropometric characteristics and body composition at baseline, and after sequential treatment with liraglutide and semaglutide.

	Patient A			Patient B			
	Baseline	Liraglutide	Semaglutide	Baseline	Liraglutide	Semaglutide	Normal values
Fasting glucose	75	67	68	81	80	84	70-110 (mg/dL)
Fasting insulin	33.7	16	15.28	16	14.7	3.26	4-24 (ng/ml)
HbA1c	5.9	5.4	5.3	5.5	5.1	5	4.0-6.0 (%)
	41	36	34.27	36.1	32.3	31	21-42(mmol/mol)
HoMA-IR	6.2	3.2	2.55	3.2	2.9	0,68	<2.5
Total cholesterol	152	155	143	217	113	205	<190 (mg/dL)
HDL-cholesterol	37	44	37.6	47	33	54	>50 (mg/dL)
LDL-cholesterol	100	96.2	87.4	156	63	137	<115 (mg/dL)
Triglycerides	75	74	92	71	81	69	<150 (mg/dL)
Platlets	214	223	206	150	175	223	150-450 (x103/µL)
AST	26	18	16	22	51	23	10-50 (mU/ml)
ALT	26	20	20	34	73	51	10-50 (mU/ml)
GGT	22	22	24	21	23	20	10-71 (U/ml)
Amilase	53	67	45	81	80	84	28-100 (U.I./l)
Lipase	55	71	53	16	14.7	3.26	13-60 (U.I./l)
Stiffenss	13 (F3)	/	8 (F2)	/	/	/	2–4 kPa
CAP	360 (S3)	/	301 (S3)	/	/	/	<237 dB/m
Fatty liver index	93		43	100		90	<60
Fibrosis-4 index	0.69		0.52	0.75		0.45	< 3.25
HSI	54		39	78		49	<36
NAFLD Fibrosis score	1.44		0.13	4.536		0.807	<1.46
HbA1c, glycated hemoglobin; HoMA-IR, homeostatic model assessment insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase, GGT, gamma-glutamyltransferase; CAP, controlled attenuation parameters; HIS, Hepatic Steatosis Index. In patient A stiffness and CAP were evaluated by transient elastography. Patient A was evaluated at baseline, after 12-month treatment with liraglutide, and after 6-months treatment with semaglutide. Patient B was evaluated at baseline, after 6-month treatment with liraglutide and after 6-months treatment with semaglutide							

Table 3: Metabolic profile, liver steatosis/fibrosis and liver indices, at baseline and after sequential treatment with liraglutide and semaglutide.

Discussion and Conclusions

We reported the effectiveness of the treatment with liraglutide, with subsequent semaglutide administration in two young females with PWS affected by hyperphagia and severe obesity. The sequential treatment with liraglutide and semaglutide induced significant reductions in hyperphagia scores and body weight, in association with improvements in insulin resistance and liver steatosis/fibrosis indices. Of interest, in both cases semaglutide showed a better performance than liraglutide in terms of weight loss and improvements in metabolic and behavioural profile. These results allow us to speculate that the reduction in hyperphagia may be attributed to both the well-known effects of GLP-1 on the hunger/satiety regulation circuit and insulin sensitivity. In our cases, sustained weight loss and reduced insulin resistance induced by liraglutide and semaglutide contributed also to reducing considerably liver damage and liver steatosis/fibrosis indices, although the direct effects of liraglutide and semaglutide in reducing the risk of MAFLD progression cannot be excluded [17]. These new findings expand the knowledge of additional therapeutic targets with GLP-1 RAs in PWS patients, who are typically unable to follow nutritional programs, and shed light on the management of life-threatening complications in PWS.

Data Availability Statement: Data generated during this study are available from the corresponding author on reasonable request.

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

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