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Effects of glucagon-like peptide-1 analogue treatment in genetic obesity: A case series

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Summary

Obesity is highly prevalent and comes with serious health burden. In a minority, a genetic cause is present which often results in therapy-resistant obesity. Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue, which has beneficial effects on satiety and weight in common obesity. We present the effects of GLP-1 analogues in adults with a molecularly proven genetic cause of their overweight or obesity. All patients were treated with liraglutide 3.0 mg daily, in addition to intensive supportive lifestyle treatment. Anthropometrics, metabolic parameters, resting energy expenditure (REE), side effects, and subjectively reported satiety and quality of life were assessed. Two patients with 16p11.2 deletion syndrome and two patients with heterozygous pathogenic melanocortin-4 receptor variants were treated. At baseline, their age ranged between 21 and 32 years and body mass index (BMI) ranged between 28.1 and 55.7 kg/m^2. At follow-up (ranges 43 weeks–12 years), a mean change in BMI and waist circumference was observed of -5.7 ± 3.8 kg/m^2 and -15.2 ± 21.1 cm, respectively. All patients achieved ≥5% weight loss, three of them lost ≥10% of their body weight. All patients reported improved quality of life and three of them reported ameliorated satiety. Moreover, improvement of glycaemic control and dyslipidaemia were seen. In two patients, REE before and during treatment was measured, which either increased (+26% of predicted REE) or decreased (−18% of predicted REE). Two patients experienced mild side effects for a brief period. In conclusion, our case series shows beneficial effects of GLP-1 analogues on weight, metabolic parameters and quality of life in all four patients with genetic obesity.

KEYWORDS
16p11.2 deletion, GLP-1 receptor agonist, melanocortin-4 receptor, quality of life, satiety, weight loss

Cornelis J. de Groot and Lotte Kleinendorst contributed equally to this study.

What is already known about this subject

- In patients with genetic obesity lifestyle interventions often fail, resulting in therapy-resistant obesity.
- Liraglutide, a glucagon-like peptide 1 (GLP-1) analogue, has beneficial effects on satiety and weight in common obesity.
- Previous studies have shown weight loss effects of liraglutide in patients with melanocortin-4 receptor variants. Data on the effects of liraglutide in other forms of genetic obesity, such as 16p11.2 deletion syndrome, have not been reported yet.

What this study adds

- To our knowledge, this is the first publication reporting beneficial effects of GLP-1 analogues in treatment of patients with obesity due to 16p11.2 deletion syndrome.
- Moreover, we confirm the weight-reducing effects in patients with genetic obesity due to pathogenic heterozygous melanocortin-4 receptor variants.
- Our data suggest that pharmacotherapy should be considered as a possible treatment option in addition to lifestyle interventions, for patients with genetic obesity.

1 | INTRODUCTION

Obesity is a complex and multifactorial disease. It is associated with numerous adverse sequelae, such as cardiovascular and metabolic disorders, various types of cancer and depression.[1] An unhealthy lifestyle is the most well-known cause of obesity. However, other factors can contribute to obesity, such as psychosocial problems, endocrine disorders, weight-inducing medication, or genetics.[2]

In recent years, an increasing number of genetic obesity disorders have been discovered. The majority of these genetic defects affect the leptin-melanocortin pathway, leading to disturbed satiety signalling and disturbances in energy balance.[3] These genetic obesity disorders are assumed to be extremely rare. However, our recent study reporting on 1230 patients with obesity, revealed a 3.9% prevalence of pathogenic genetic obesity disorders and an additional 5.4% prevalence of variants of uncertain significance in obesity-associated genes together with a clinical phenotype of genetic obesity.[4] Moreover, a recent study reported a 0.3% prevalence of *melanocortin 4 receptor* (*MC4R*) deficiency in a large, representative birth cohort.[5] This makes *MC4R* deficiency the most common cause of genetic obesity. Clinical features of *MC4R* deficiency are hyperphagia, early-onset obesity, hyperinsulinemia and an accelerated linear growth during childhood.[6,7] The second most common cause of genetic obesity is a 16p11.2 deletion.[8] The 16p11.2 microdeletion has a variable phenotype, including intellectual disability, speech impairment, autism spectrum disorder (ASD), epileptic seizures and in 50% of the patients' obesity.[8]

A study investigating the effect of a lifestyle intervention performed in children with pathogenic *MC4R* variants, confirmed our clinical experience that little or only short-term effects of lifestyle treatment is seen in patients with genetic obesity disorders.[9] Moreover, bariatric surgery may be less successful in certain types of genetic obesity.[3,10] Therefore, there is a need for additional pharmacotherapy targeting the increased weight, as well as the hyperphagia.

In recent years, several new anti-obesity drugs have become available for common obesity. Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue, which was primarily developed for the treatment of type 2 diabetes (T2D). It stimulates postprandial insulin secretion and suppresses glucagon secretion.[11] Moreover, this incretin-based therapy has anorexigenic effects at a dosage of 3.0 mg in common obesity. These effects altogether resulted in a clinically relevant weight loss of at least −5% in 63.2% of the participants.[12] Recent small studies of Iepsen et al. reported results of liraglutide 3.0 mg treatment in patients with *MC4R* variants: a weight loss of −5.7% in 14 patients with heterozygous *MC4R* deficiency and −6.4% weight loss in a patient with homozygous *MC4R* deficiency.[13,14] Moreover, several studies describe beneficial effects of GLP-1 analogues on satiety and/or weight loss in patients with Prader-Willi syndrome.[15,16] Since data on the effects of GLP-1 analogues in other forms of genetic obesity are unavailable, we here present our first clinical experiences of GLP-1 analogues in two patients with a 16p11.2 deletion and two patients with heterozygous *MC4R* deficiency.

2 | METHODS

2.1 | Study population

In this case series, adult patients with a molecularly confirmed genetic obesity disorder, who were treated with GLP-1 analogues as add-on therapy to an optimized lifestyle, are described. Adults were eligible for GLP-1 analogue treatment if they met the following criteria: obesity, defined as a body mass index (BMI) ≥30 kg/m^2 or a BMI ≥27 kg/m^2 combined with weight-related co-morbidities or hyperphagia; and a poor response to intensive supportive lifestyle treatment. Liraglutide was initiated at a dose of 0.6 mg daily for 1 week, followed by a weekly increase of the dose to the maximum tolerated dose or the 3.0 mg dose within 5 weeks, according to the manufacturer's protocol.[17] Intensive supportive lifestyle treatment was continued during treatment.

2.2 | Study procedures

Anthropometrics (body weight, height and waist circumference), biochemical evaluations (including fasting glucose, HbA1c, lipids and liver enzymes), resting energy expenditure (REE), bio-electrical impedance (BIA), and adverse effects were assessed at baseline and during follow-up visits. Predicted values of REE were calculated using the Harris & Benedict formula.[18] After 12 weeks of treatment using the maximum effective dose, the evaluation of GLP-1 analogue treatment was done at the follow-up visit, according to the standardized protocol. If the patient achieved a clinical relevant −5% weight loss or improvement in metabolic factors, such as improved glycaemic control or dyslipidaemia, the patient could continue the therapy. Since data were derived retrospectively from the patient's medical records, follow-up intervals and availability of clinical data varied.

2.3 | Statistical procedures

Data were analysed using SPSS version 25.0 [IBM]. Data are presented as mean and standard deviation or as ranges (minimum–maximum).

3 | CASES

The clinical course of four patients (three female, one male) with a genetic obesity disorder and GLP-1 analogue treatment is described. At baseline, their age and BMI ranged between 21–32 years and 28.1–55.7 kg/m^2. The follow-up duration ranged between 43 weeks and 12 years.

3.1 | Patient 1

Patient 1 is a 28-year-old male, with early-onset hyperphagia without childhood obesity due to strict parental lifestyle measurements. At the age of six, he was diagnosed with ASD. Due to behavioural problems, treatment with haloperidol and pipamperone was started at the age of 11. Subsequently, from the age of 15 onwards, he developed obesity. At the age of 20, a de novo heterozygous ∼540 kb loss at the short arm of chromosome 16 was identified, compliant with proximal 16p11.2 deletion syndrome, explaining the patient's phenotype. At the age of 23 with a weight of 107.4 kg, a BMI of 33.3 kg/m^2 and waist circumference of 94 cm, he was evaluated at our obesity centre. He immediately started a strict diet aimed at subjects with intellectual impairments or ASD. This diet regime, guided by dieticians with ample experience of genetic obesity, makes use of dots (25 kcal per dot) to maintain a healthy diet.[19] This personalized guidance, in combination with stopping of the antipsychotics, resulted in significant weight loss of −27 kg, with a limited weight regain of +6 kg, after 4.5 years. Given that the patient still was overweight and suffered from hyperphagia, treatment with liraglutide was initiated. Biochemical analysis prior to liraglutide treatment showed dyslipidaemia (Table 1). Liraglutide treatment was initiated with a weekly increasing dosing schedule to 3.0 mg daily, without significant side effects. After 17 weeks of treatment an additional weight reduction of −8.5 kg (−9.8%) was seen. Moreover, he consistently reported improved satiety feelings and biochemical analysis revealed an improved dyslipidaemia. After 44 weeks of liraglutide, his weight remained stable resulting in a final weight loss of −10.5 kg (−12.1%) and BMI of 24.7 kg/m^2 (Table 2). His waist circumference decreased by −4 cm. See Figure 1 for the absolute changes in body weight during course of treatment.

3.2 | Patient 2

Patient 2 is a 44-year-old female. She had a normal birth weight of 3200 g and developed obesity and signs of hyperphagia in infancy. During childhood, she had learning problems. At age nine, she had a BMI of 25.5 kg/m^2 (+3.1 SD) therefore dietary guidance was started. Because of polyneuropathy and catamenial epilepsy, she was treated with amitriptyline, carbamazepine and orgametril. When she was referred at the age of 31 to an endocrinologist because of T2D, she had a weight of 113.2 kg with a BMI of 38.3 kg/m^2. Biochemical analysis showed elevated blood glucose levels, HbA1c and elevated liver enzymes (Table 1). She was successfully treated with twice daily 850 mg metformin and twice daily 10 μg exenatide, one of the early GLP-1 analogues, and lost −26.5 kg of weight (−23.4%). Although her quality of life improved, her hyperphagia remained unchanged. She did not experience any side effects. In the following years, an additional twice daily 80 mg gliclazide was started by her general practitioner because of fluctuating blood glucose levels and HbA1c. At the age of 39, the exenatide was replaced for liraglutide. This was increased to the final dose of once a day 1.8 mg, the dose recommended for T2D. She continued with metformin, gliclazide, amitriptyline, carbamazepine and orgametril treatment. At the age of 44, she was referred to a clinical geneticist to find a syndromic cause of her problems. She was diagnosed with distal 16p11.2 deletion syndrome, caused by a ∼218 kb deletion including the *SH2B1* gene, explaining the patient's phenotype. After 12 years of GLP-1 analogue treatment, biochemical analysis showed improved glycaemic control. Her weight stabilized at around 82 kg, resulting in a total loss of −31.2 kg of body weight (−27.6%) with a BMI of 27.7 kg/m^2 (Table 2). See Figure 1 for the absolute changes in body weight during course of treatment. Recently, she has been referred to the dietician again to continue lifestyle guidance during GLP-1 analogue treatment.

3.3 | Patient 3

Patient 3 is a 22-year-old female. The neonatal period was uncomplicated with normal gestational age and birthweight. In early infancy, she developed obesity despite strict lifestyle measures, without hyperphagia. Because optimizing lifestyle did not result in any weight loss, genetic testing was performed at the age of 16 showing a heterozygous pathogenic *MC4R* variant (NM_005912.2 [*MC4R*]:

TABLE 1 Baseline characteristics of $n = 4$ patients with genetic obesity before start of glucagon-like peptide-1 analogue treatment

Patient ID	Sex	Genetic diagnosis	AoO obesity, years	Age, years	Weight, kg	BMI, kg/m^2	WC, cm	REE, kcal/day (% of predicted)[a]	Fasting glucose, mmol/L	HbA1c, mmol/mol	Dyslipidaemia[b]	Elevated liver enzymes[c]
1	M	16p11.2 deletion	15	28	86.5	28.1	94	NA	4.9	31	Yes	No
2	F	16p11.2 deletion	9	32	113.2	38.3	NA	NA	13.2	70	No	Yes
3	F	MC4R heterozygous	1	21	114	38.1	123.5	1997 (−5.3)[d]	5.1	29	No	No
4	F	MC4R heterozygous	5	28	188.7	55.7	129	1738 (−34)	6.4	38	Yes	No

Abbreviations: AoO, age of onset; BMI, body mass index; F, female; M, male; MC4R, melanocortin-4 receptor; NA, not available; REE, resting energy expenditure; WC, waist circumference.
[a]Measured by indirect calorimetry, reference values were calculated using the Harris & Benedict formula.
[b]Presence dyslipidaemia is defined as triglycerides >2.0 mmol/L, total cholesterol >5 mmol/L, HDL-cholesterol <1.0 mmol/L or LDL-cholesterol >3.0 mmol/L.
[c]Elevated liver enzymes is defined as ALAT > 45 U/L, ASAT > 35 U/L, gamma-GT > 55 U/L or alkaline phosphatase >115 U/L.
[d]Measured at age of 16.8, predicted value was calculated using the Schofield formula.

TABLE 2 Outcome measures in $n = 4$ patients with genetic obesity at follow-up during glucagon-like peptide-1 analogue treatment

Patient ID	Treatment duration at follow-up, weeks (w) or years (y)	Weight, kg	Δ, kg (%)	BMI, kg/m^2	Δ, kg/m^2	WC, cm	Δ, cm	REE, kcal/day (% of predicted)[a]	Δ, % of predicted REE	Fasting glucose, mmol/L	HbA1c, mmol/mol	Dyslipidaemia[b]	Elevated liver enzymes[c]
1	44w	76	−10.5 (−12.1)	24.7	−3.4	90	−4	NA	NA	4.9	33	Improved[d]	No
2	12y	82	−31.2 (−27.6)	27.7	−10.6	NA	NA	NA	NA	6.7	51	No	NA
3	66w	95.9	−18.1 (−15.9)	31.3	−6.8	84	−39.5	1498 (−18)	−12.7%	5.2	29	No	No
4	43w	177.2	11.5 (−6.1)	53.6	−2.1	127	−2	2381 (−6)	+26%	5.2	36	Yes[e]	No

Abbreviations: BMI, body mass index; NA, not available; REE, resting energy expenditure; WC, waist circumference.
[a]Measured by indirect calorimetry, predicted values were calculated using the Harris & Benedict formula.
[b]Presence dyslipidaemia is defined as triglycerides >2.0 mmol/L, total cholesterol >5 mmol/L, HDL-cholesterol <1.0 mmol/L or LDL-cholesterol >3.0 mmol/L.
[c]Elevated liver enzymes is defined as ALAT > 45 U/L, ASAT > 35 U/L, gamma-GT > 55 U/L or alkaline phosphatase >115 U/L.
[d]Triglycerides decreased from 3.85 to 3.2 mmol/L, cholesterol decreased from 4.8 to 4.5 mmol/L, LDL decreased from 2.67 to 2.08 mmol/L.
[e]Triglycerides decreased from 2.71 to 2.00 mmol/L, total cholesterol increased from 5.5 to 5.9 mmol/L, LDL increased from 3.88 to 4.23 mmol/L.

c.105C > A; p.(Tyr35*) affecting the function of the MC4 receptor.[6] Her baseline weight, BMI and waist circumference were 114 kg, 38.1 kg/m^2, 123.5 cm, respectively. Prior to treatment, her REE was determined which was 1997 kcal per day (−5.3% lower than predicted). Biochemical analysis at baseline showed no abnormalities (Table 1). She started using liraglutide 0.6 mg daily which was weekly increased to 3.0 mg daily. She experienced known side effects (mainly nausea and vomiting) at the maximum dose of 3.0 mg, which led to a 6-day pause in treatment. Afterwards, liraglutide was re-started at a dose of 0.6 mg and increased to her maximum tolerated dose of 2.4 mg daily without significant side effects. At approximately 17 weeks after the first start of liraglutide, she lost −16 kg of body weight (−14%). After 66 weeks of treatment, her weight stabilized at 95.9 kg, resulting in a total loss of −18.1 kg of body weight (−15.9%, Table 2). See Figure 1 for the absolute changes in body weight during course of treatment. Her waist circumference decreased by −39.5 cm. She subjectively reported markedly increased satiety and increased quality of life. At follow-up, the biochemical analysis did not show abnormalities, similar to baseline. Her REE after 66 weeks of liraglutide was 1498 kcal/day, which was −18% lower than predicted and −12.7% lower compared to baseline (Table 2).

3.4 | Patient 4

Patient 4 is a 29-year-old female. She developed hyperphagia and progressive, therapy-resistant obesity from the age of 5 and onwards. At the age of 13, a heterozygous pathogenic *MC4R* variant was identified NM_005912.3 [*MC4R*]: c.750_751del; p.(Ile251Trpfs*34), resulting in total loss of function of the *MC4R*.[7] She initiated a very stringent calorie restricted and sporting treatment program, resulting in a weight loss of −56 kg within 9 months, with a weight regain of +84 kg in the upcoming year. Afterwards, she was unsuccessfully treated in a specialized centre for binge eating disorders to control her hyperphagia. Despite these treatments, at the age of 28, she had a weight of 188.7 kg, a BMI of 56.7 kg/m^2 and waist circumference of 129 cm and was therefore referred to our academic obesity centre. Her REE before initiation of liraglutide treatment was 1738 kcal/day, which was −34% lower than predicted. BIA at baseline revealed an increased fat mass and lean body mass of 100.5 kg (53.5%) and 88.2 (46.7%), respectively. Biochemical analysis showed increased fasting glucose and dyslipidaemia (Table 1). Treatment was initiated and dosing was increased to 3.0 mg within 5 weeks. She briefly experienced nausea, stomach pain and headache. After 18 weeks, her weight decreased by −9.5 kg (−5%) resulting in a BMI of 54.2 kg/m^2. Her satiety feelings and quality of life improved. Biochemical analysis showed a normalized fasting glucose and improved lipids. Of note, from 8 weeks of treatment onwards the COVID pandemic occurred and related lockdown measures were taken including the closure of her gym, which she normally frequently visited. Despite these circumstancing which could have led to less than expected weight loss, her weight continued to decrease to 177.2 kg (−11.5 kg, −6.1%), her BMI to 53.6 kg/m^2 and her waist circumference to 127 cm (−2 cm) after 43 weeks of treatment with COVID-19 restrictions

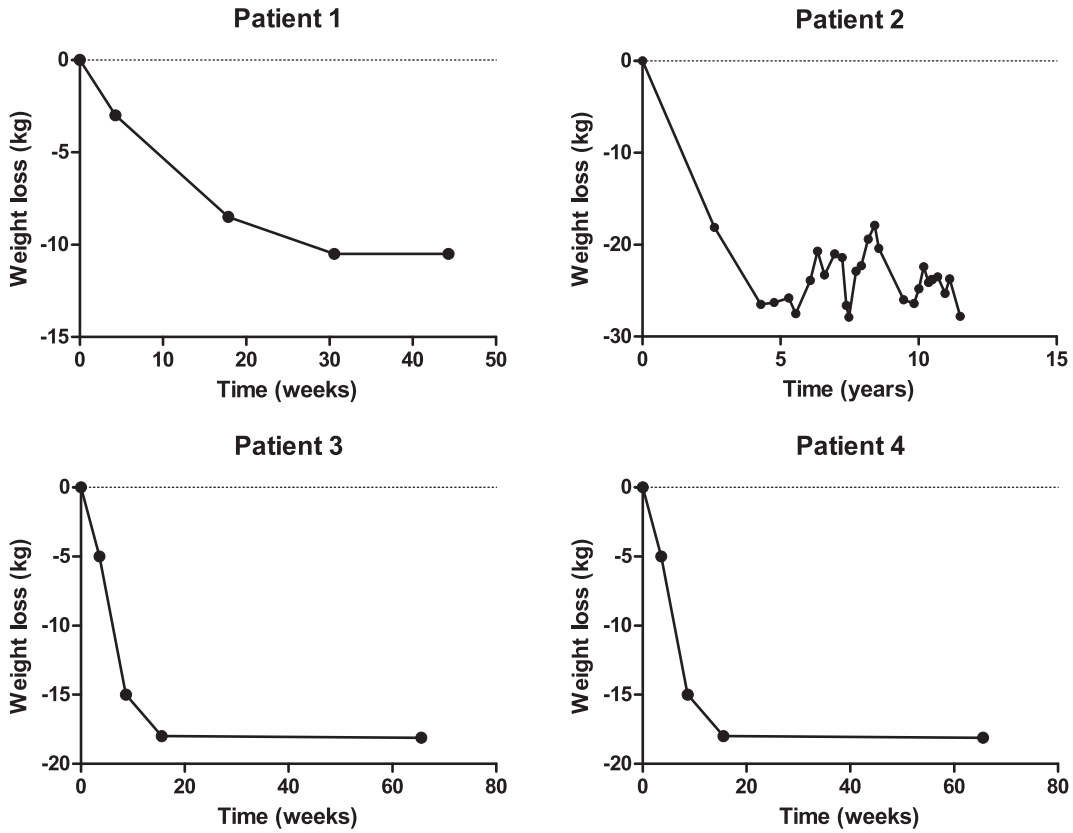

FIGURE 1 Absolute change in body weight per patient during glucagon-like peptide-1 analogue treatment

(Table 2). See Figure 1 for the absolute changes in body weight during course of treatment. Biochemical analysis at follow-up reported no clinical relevant abnormalities. Her REE was determined at 2381 kcal/day, which was as predicted and +26% higher compared to baseline (Table 2). BIA at end of follow-up reported a decrease of mainly fat mass (−9.5 kg, 51.4%) and also lean body mass (−2 kg, 48.6%).

4 | DISCUSSION

We here describe four patients with overweight or severe obesity caused by genetic obesity disorders (two patients with 16p11.2 deletion syndrome and two patients with a heterozygous pathogenic *MC4R* variant) who were successfully treated with GLP-1 analogues. Their follow-up time varied from 10 months to 12 years, their weight loss varied between −6.1% and −27.6%, their decrease in waist circumference ranged between −2 and −39.5 cm, and their metabolic parameters, such as glycaemic control or dyslipidaemia, also improved. Three of the four patients reported an improved satiety, of which they indicated that it significantly contributed to a better quality of life. Before GLP-1 analogue treatment, their hyperphagia and/or impaired satiety had a large impact on their lives, as these patients reported preoccupations with food and extreme focus on their continuous attempts to restrict eating. All patients also subjectively reported improved quality of life in other aspects, such as physical fitness and mental wellbeing. Two patients reported short-term side effects, such as nausea and stomach pain, which are well-known for liraglutide and self-limiting. In two patients changes in REE were observed.

Little is known about the effects of GLP-1 analogue treatment in patients with genetic obesity. To our knowledge, this is the first publication reporting beneficial effects of GLP-1 analogues in obesity treatment of patients with 16p11.2 deletion syndrome. As to date, no literature about effective pharmacotherapy treatment for obesity in these patients is available yet. Thus far, one small study has investigated the effect of 16 weeks of liraglutide treatment in 14 patients with heterozygous pathogenic *MC4R* variants, showing a reduction in weight (−6%), waist circumference, percentage fat mass and decreased fasting glucose.[13] Moreover, a recent case report of a patient with a homozygous pathogenic *MC4R* variant showed similar results.[14] These outcomes are in line with the results of our cases with heterozygous pathogenic *MC4R* variants. Furthermore, we add that subjectively reported quality of life of these patients also improves. Our results seem promising since the beneficial effect of GLP-1 analogue treatment might also apply to patients with other types of genetic obesity, for whom no targeted treatment is available yet.

Liraglutide, a well-known antidiabetic agent, stimulates the glucose-dependent secretion of insulin in the beta-cells of the pancreas and suppresses the secretion of glucagon, resulting in lower blood glucose levels.[20] This GLP-1 analogue also has anorexigenic effects, contributing to weight loss in common obesity. The reduction in food intake and improved satiety and satiation can be partially explained by the reduced gastrointestinal motility.[20] The direct mechanism of action of liraglutide on the brain remains unclear. Two studies showed that liraglutide stimulates anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons and inhibits orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) neurons in the arcuate nucleus in the hypothalamus. This could be a possible mechanism through which liraglutide might induce satiety.[21,22] Interestingly, even though three of our cases have a deficient leptin-melanocortin pathway, they experienced weight loss and improved satiety during GLP-1 analogue treatment. This was also observed in the two abovementioned studies of Iepsen et al. reporting on the effects of liraglutide treatment in patients with heterozygous pathogenic *MC4R* variants and, even more importantly, in a patient with a homozygous pathogenic *MC4R* variant.[13,14] Moreover, in mice neither the mc4r nor the serotonin 5-ht2c receptor seemed to be required for the anorexigenic effect of liraglutide.[23] It is thus likely that liraglutide also affects other pathways, which bypass the *MC4R* dependent pathway. Further supporting this notion are rat studies reporting direct activation of GLP-1 receptors on GABA neurons in the nucleus tractus solitarius or via direct activation of the periventricular neurons.[24,25] Moreover, functional magnetic resonance imaging has shown a decreased activity of appetite- and reward-related areas of the brain (insula, amygdala, orbitofrontal cortex and putamen) during GLP-1 analogue treatment in patients with obesity.[26] Concluding, evidence suggests that the effects of GLP-1 analogues are mediated via multiple neuronal populations and nuclei, which can explain the beneficial effects of GLP-1 analogue treatment in our patients with leptin-melanocortin pathway defects. In three of the four patients with genetic obesity, we observed an exaggerated response to GLP-1 analogues with respect to weight loss. Whether this was caused by the effects on the appetite-regulating brain areas in these patients with hyperphagia due to their genetic defect warrants further investigation.

In two of our patients, the REE was measured before and after liraglutide treatment. The difference in percentage of predicted REE before and during treatment was −12.7% in patient 1 and +26% in patient 2. However, in patient 1, the REE was measured using two different types of indirect calorimeters, which could have impacted the outcome. Moreover, the previously reported physiological decreases of REE during puberty may have negatively influenced the REE before treatment, as this patient was first measured at the age of 16 and then measured during adulthood.[27] Furthermore, conservation of energy due to caloric restriction, also known as metabolic adaptation, might explain the decrease in REE of patient 1.[28] This was, however, not observed in patient 2. It is hypothesized that liraglutide can affect energy expenditure, as studies have shown the effects of liraglutide on the POMC, NPY and AgRP neurons in the hypothalamus. Via release of alpha-MSH, beta-MSH and c-MSH, the *MC4R* is stimulated leading to an increased satiety and increased energy expenditure.[22] Moreover, a recent study showed activation of brown adipose tissue, which is involved in energy metabolism, in nondiabetic adults with normal weight treated with GLP-1 analogues. However, this did not affect their REE.[29] No other studies have reported a clear effect of liraglutide treatment on REE, some report decreased REE,[20,30] some report increased REE,[31,32] and some report no effects,[29] which is similar to our findings.

The present, however limited, observations show promising results of GLP-1 analogue treatment in patients with genetic obesity. This could offer patients a less invasive therapeutic option that is, in contrast to bariatric surgery, also reversible. These promising results pose the question if pharmacotherapy, as an adjunct to combined lifestyle interventions, could acquire a place in the standard obesity treatment protocols of patients with genetic obesity. This could be as primary treatment, as condition-improving step before bariatric surgery, or to optimize weight loss and prevent weight regain after bariatric surgery. Importantly, treatment with liraglutide is generally recommended to discontinue if the patient has not achieved at least 5% weight loss after 12 weeks at the maximum effective dose. Such a test period seems also important in patients with a (suspected) underlying genetic cause of obesity, although weight maintenance rather than otherwise progressive weight gain despite stringent lifestyle measures might also be a goal in some patients with genetic obesity. Currently, most patients with genetic obesity are probably not diagnosed as such and many undergo bariatric surgery because of severe therapy-resistant obesity. However, bariatric surgery is often not easily reversible and carries some long-term side effects.[33] Accordingly, pharmacotherapy seems in some patients a good first option to consider. At the moment, there is no specific treatment advice for patients with genetic obesity in most obesity guidelines. In that light, it is interesting that other anti-obesity agents, such as setmelanotide, are on the brink of becoming available for some of these patients as well, although this may not be suitable to all gene defects affecting the leptin-melanocortin pathway.[34,35] In the future, it might even be conceivable to combine different types of anti-obesity agents, such as GLP-1 analogues (e.g. liraglutide or semaglutide), naltrexone-bupropion, phentermine-topiramate, setmelanotide or other drugs currently under development.[36] This could result in possible synergistic effects mediated through different pathways, e.g. leptin-melanocortin pathway and hedonistic pathway, based on the patients' underlying condition.

Since we only report a limited number of cases, future research should focus on including larger numbers of patients with different types of molecularly confirmed genetic obesity disorders. Since it is challenging to include a sufficient number of patients with these rare genetic obesity disorders, we here demonstrate the importance of case series. To offer further insights in underlying mechanisms of action and predictors of therapeutic effects, we recommend that these studies entail structural standardized measuring of anthropometrics, body composition, biochemical analyses, REE and standardized questionnaires for evaluation of satiety and quality of life.

In conclusion, our case series shows beneficial effects of GLP-1 analogues on weight loss, metabolic parameters, such as glycaemic control or dyslipidaemia, and satiety in patients with obesity resulting from a 16p11.2 deletion or heterozygous pathogenic *MC4R* variants. Our findings suggest that GLP-1 analogues can be an effective treatment option, in addition to a healthy lifestyle, for patients with a molecularly confirmed genetic obesity disorder. Therefore, we advocate that pharmacotherapy should be considered as a possible treatment option in combination with lifestyle interventions for patients with genetic obesity.

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CONFLICT OF INTEREST

All authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Mila S. Welling was responsible for data collection, data analysis, data interpretation, writing of the first draft and the final adjustments for this manuscript. Elisabeth F. C. van Rossum, Cornelis J. de Groot and Lotte Kleinendorst were responsible for the concept of the project, data collection, interpretation of the data, patient care and revising the manuscript critically. Eline S. van der Valk, Jan Steven Burgerhart, Bibian van der Voorn, Erica L. T. van den Akker and Mieke M. van Haelst contributed to the hypothesis, treatment guidance and interpretation of the results of the study. All authors contributed to the writing of the manuscript, made critical comments and approved the final version.

ETHICAL APPROVAL

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. GLP-1 analogue treatment was initiated in the context of routine patient care; therefore, no approval by the ethics committee was required for this retrospective analysis. All four patients have given their written informed consent to publish their case.

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