Obesity Facts

Case Report

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Rapid Emergence of Appetite and Hunger Resulting in Weight Gain and Improvement of Eating Disorder Symptomatology during and after Short-Term Off-Label Metreleptin Treatment of a Patient with Anorexia Nervosa

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Leptin · Anorexia nervosa · Antidepressant · Hunger · Starvation

Abstract
Off-label treatment of a 15-year-old female patient with anorexia nervosa (AN) with human recombinant leptin (metreleptin) for nine days was associated with self-reported increments of appetite and hunger resulting in rapid weight gain and substantial improvement of eating disorder cognitions and of depression. The results further substantiate the effects of metreleptin on both AN and depression. We contrast these results with the widespread view that leptin is an anorexigenic hormone. Randomized controlled trials are warranted to confirm the described effects.

Introduction

Anorexia nervosa (AN) remains a debilitating disorder that, due to underweight entailing symptoms of starvation, poses a substantial threat to somatic and psychological maturation during adolescence and early adulthood. The fact that no medications have been approved for its treatment all the more underscores the urgent need for research into beneficial treatments of AN [1]. Based on the hypothesis that metreleptin improves starvation-related mental symptoms [2], we treated single patients with AN with human recombinant leptin (metreleptin) [3, 4]. Substantial improvements were observed in three of the four patients treated off-label for between six and 24 days. In two of these patients, self-rated appetite and hunger intermittently increased.

Clearly, such an effect is not in line with the assumed anorexigenic role of the adipokine leptin. According to this assumption [5], leptin mediates resistance to obesity by its levels rising in response to a positive energy balance. Indeed, application of recombinant leptin to both wild-type mice [6] and lean humans [7] entails body weight

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loss and, in particular, loss of fat mass. However, in the human subjects, the mean weight loss was only approximately one kg upon treatment for 12 weeks; some of the lean females even gained weight [7]. Similarly, patients with generalized lipodystrophy only infrequently need to stop metreleptin treatment because of weight loss. Such patients do, however, report an improved satiation and satiety after meals within one to two days after initiation of dosing [8, 9]. Treatment of obese wild-type mice and of humans with obesity with recombinant leptin had only minimal effects on body weight [5]. In conclusion, application of exogenous leptin can affect feelings of satiation and satiety in humans. However, substantial weight loss is observed regularly only in patients with inborn congenital leptin deficiency [10, 11]. Clearly, the assumed role of leptin in energy balance and weight regulation requires a reassessment [5].

Based on findings indicative of a major role of hypoleptinemia in the neuroendocrine adaptation to starvation, Ahima and colleagues postulated that this adaptation represents the major function of the hormone leptin [12]. Sub-physiological serum levels of leptin represent a key endocrine feature of AN [13–15]. Similar to findings in rodents [12], hypoleptinemia triggers the down-regulation of the hypothalamus-pituitary-gonadal axis, entailing reduced levels of sex hormones in both male and female patients with AN [16, 17].

The neuroendocrinology of appetite is based on complex neurobiological pathways with links between different regions of the central nervous system and between the central nervous system and peripheral tissues and organs including, for instance, the adipose tissue and the gut-brain axis [18]. Because of the intertwining of the symptoms of AN with those of starvation [15], comparisons of assessments of hunger and appetite with those observed upon starvation and fasting unrelated to AN are warranted. In the 36 male participants of the Minnesota Starvation Experiment [19] conducted in 1944/1945, hunger was prominent. However, the mean of self-rated appetite upon use of visual analogue scales was merely three out of five (1 = "more"; 5 = "extremely more") during the final week of the 24-week long starvation phase ($n = 34$). Mean ratings for "palatability of food" actually decreased slightly between weeks 12 and 24. Ratings for "hunger pain" remained below a mean score of two at both weeks 12 and 24. During therapeutic fasting periods of between four and 21 days in 1,422 subjects, hunger was an infrequent complaint only [20].

Only a limited amount of studies with controversial results have assessed appetite and hunger in patients with AN [21]; Klastrup et al. [21] discuss different reasons for our lack of knowledge as to what extent appetite is altered in these patients. For example, starvation-induced delayed gastric emptying and constipation may cause nausea and early satiety. Overall, the assessment of appetite in patients with AN is challenging due to a possible denial of appetitive perceptions or a marked inability to process internal hunger and satiety signals [21]. Without doubt, preoccupation with food is a common symptom in patients [22] who may seek to cook for others and experience reward from reading recipes or viewing food-related pictures and videos. Similar to the situation of patients with acute AN [23], the preoccupation with food/eating was omnipresent in the participants of the Minnesota Starvation Experiment [19]. In conclusion, preoccupation with food/eating is clearly an overarching symptom; evidence suggests that it is induced by starvation. The situation regarding hunger and appetite is less clear. Both hunger and appetite are likely affected by the degree of starvation; many behavioural responses to a restricted food intake follow a hump-shaped (inverted U-shaped) pattern depending on the degree of starvation [24]. Inter-individual variation of the hunger/appetite response to starvation/fasting also appears likely. In this case report we focus on an increase in self-reported appetite and hunger in an adolescent with AN, which was triggered by short-term metreleptin treatment.

Case Report

The currently 15-year-old female patient R was initially referred as an outpatient at age 14 (BMI of 16.3 kg/m^2; 4th sex- and age-matched BMI-centile; online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000527386) after a rapid weight loss of 15 kg within five months (premorbid BMI 22.4 kg/m^2; 78th BMI-centile) fulfilling DSM-5 diagnostic criteria for the restricting type of AN. Patient R skipped meals, showed food picking/nibbling, and increased meal lengths; self-reported daily caloric intake was <500 kcal. She exercised excessively, was amenorrheic (menarche at age 12; time at cessation of menstruation not remembered precisely), and had night-time bradycardia (38–44 beats/min). She felt constantly cold, tired, weak, irritable, and depressed.

The patient was initially admitted to the acute psychiatric ward (BMI 16.10 kg/m^2) for seven days and, after a brief period at home (nine days; online suppl. Fig. 1), readmitted to the inpatient eating disorder unit (16.69 kg/m^2). Treatment consisted of individual and family-based psychotherapy and medication (olanzapine 2.5 mg twice daily). During the three-month-long inpatient treatment, patient R gained 6.4 kg (19.2 kg/m^2). In the following two weeks after discharge, patient R ate two meals a day, lost three kg, reported repeated non-suicidal self-injury (superficial cutting), weight phobia, and tiredness; she spent most of her time in bed. Upon

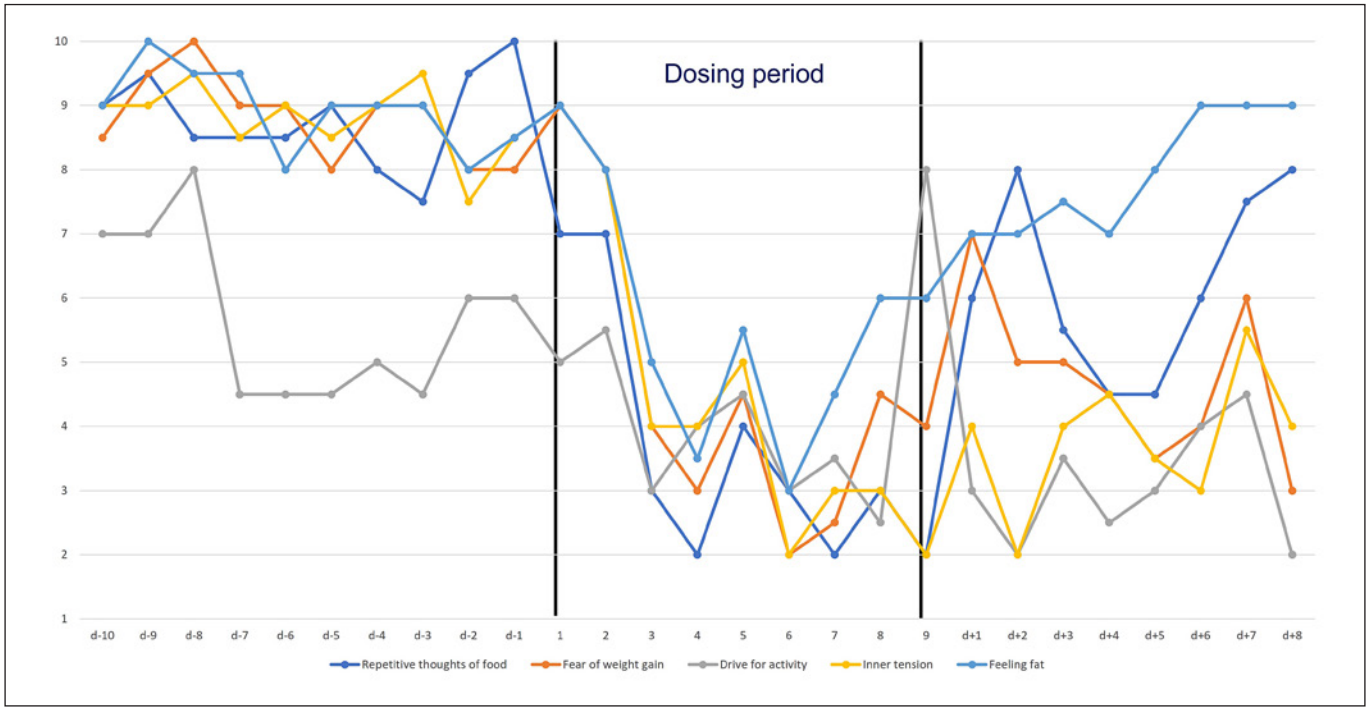

Fig. 1. Means of eating disorder associated cognitions and emotions assessed twice daily with visual analogue scales (range 1–10) prior to, during, and after the 9-day dosing period.

readmission, she received nasogastric tube feeding for four days in light of her inability to eat a sufficient amount of food; her olanzapine dosage was increased to 7.5 mg/day. She discharged herself against medical advice on day five. Back at home, the patient further restricted her food intake and lost another three kg. She was readmitted 16 days later (17.05 kg/m^2). She again received nasogastric tube feeding voluntarily at first and when she withdrew her consent after ten days and stopped fluid and food intake completely and manipulated the tube, received treatment under restraint via court order for another 15 days. All efforts to re-establish voluntary tube feeding or weaning off the tube failed. To reduce anxiety, patient R received 2.5 mg diazepam with each tube feeding. In light of pronounced symptoms of depression including suicidal ideation, she was also started on escitalopram 5 mg five days before discharge. In light of improved mood and motivation to study in school, the olanzapine dosage was reduced to 5 mg daily. Due to the overall improvement, there was a growing ethical conflict of the therapeutic team regarding feeding under restraint leading to the discontinuation of inpatient treatment after a total stay of 28 days (BMI at discharge: 18.4 kg/m^2).

In subsequent regular outpatient contacts, patient R reported eating nothing except fruits, protein bars, and puddings and porridge with almond milk. She described an increasing urge to harm herself and soon started losing weight again (two kg). Repeatedly determined serum leptin levels fluctuated between subnormal and high (1.7–7.7 ng/mL; online suppl. Table 1), reflecting changes in both energy intake and fat mass.

Methods

In light of the severe eating disorder symptomatology including the potential need to again restrain the patient to ensure adequate energy intake, both the patient and her parents agreed to an off-label treatment with metreleptin (serum leptin level on dosing day 1: 1.6 ng/mL) and provided written informed consent in accordance with the latest version of the Declaration of Helsinki [25]. In extended and repeated consultations over a period of several weeks, the patient and her mother received information on the suggested off-label treatment based on the known side effects of metreleptin and our previous experience in treatment of patients with AN [3, 4]. The patient's ability to understand relevant medical information was assessed continuously throughout the process. The family's main concern regarded treatment failure and potential side effects. We had the impression that both the patient and her mother made well-considered and independent decisions upon provision of written consent.

The safety of metreleptin was assessed in patients with lipodystrophy (open-label, non-controlled Phase-II trials). The most common side effects are hypoglycaemia, decrease in weight, injection site reactions, and formation of neutralising antibodies. Three cases of T-cell lymphoma occurred in patients with acquired generalized lipodystrophy (AGL; because of the known association of AGL with lymphoma, the causality is unclear; nevertheless, FDA requires a so-called Risk Evaluation and Mitigation Strategy [REMS] and EMA an equivalent so-called Risk Management Plan for metreleptin). Caution is advised for use of the product in pa-

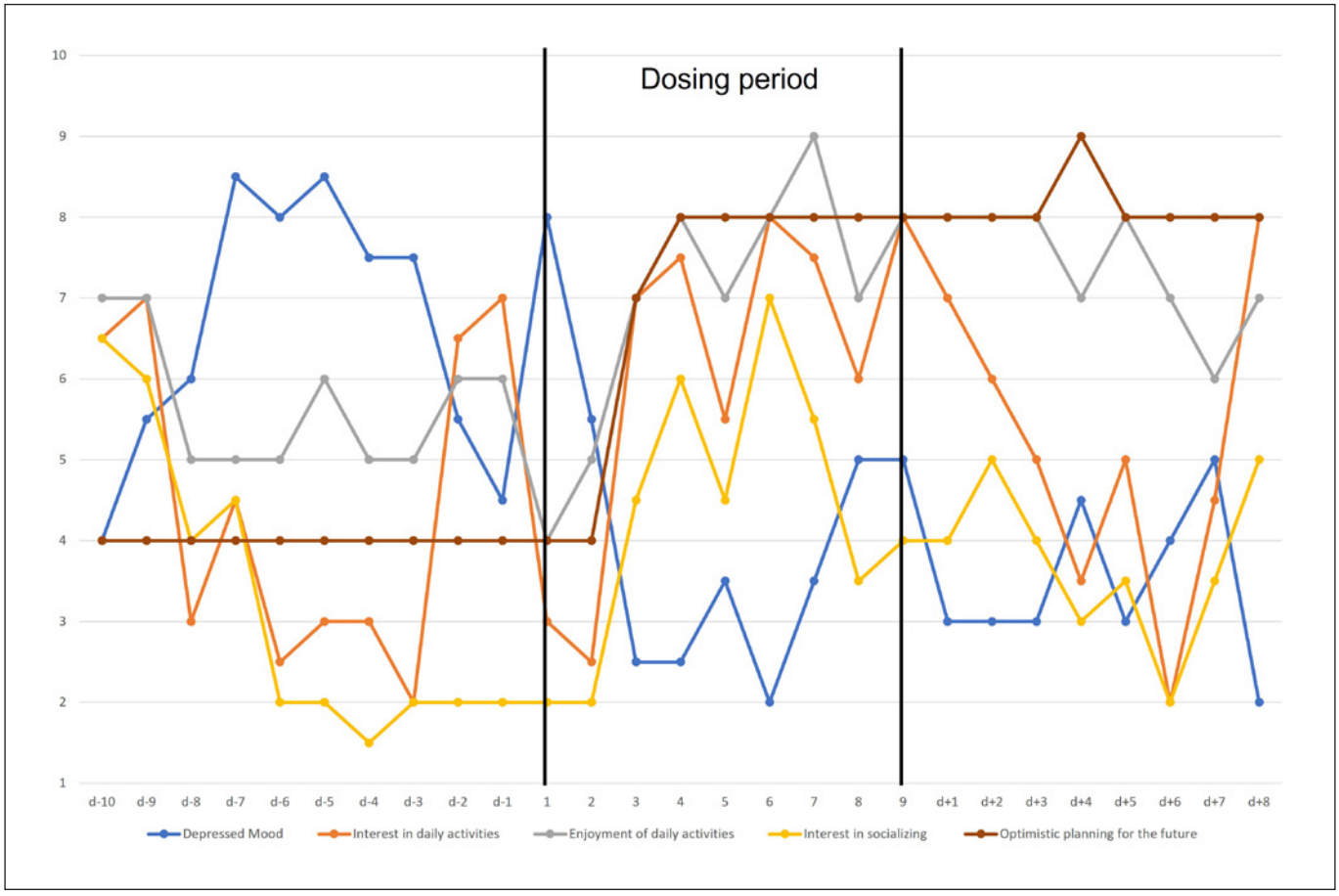

Fig. 2. Means of depressive cognitions and emotions assessed twice daily with visual analogue scales (range 1–10) prior to, during, and after the 9-day dosing period.

tients with significant haematological abnormalities (including leukopenia, neutropenia, bone marrow abnormalities, lymphoma, and/or lymphadenopathy). The patient was hospitalized for the first four dosing days, and the final five metreleptin dosages were applied on an outpatient basis.

Metreleptin dosages of 3–5.8 mg/day (5.8 mg: d1–d8; 3 mg: d9) were applied subcutaneously at 9:00 a.m. Similar to previously published case reports [3, 4], we used visual analogue scales (VAS; daily means of morning and evening scores) to assess psychopathology. The patient also self-rated depressive symptoms and eating disorder-specific symptomatology using the German versions of Beck Depression Inventory-II [26] and Eating Disorder Inventory-2 [27] on d1 and d4 of the dosing period. EDI-2 is a self-report questionnaire consisting of 91 items on eleven subscales designed for the assessment of attitudinal and behavioural dimensions relevant to AN and bulimia nervosa [27]. The EDI-2 is used worldwide as a screening and evaluation tool for eating disorders and to measure treatment effects and outcomes. Serum leptin levels were repeatedly measured at 9 a.m.

Psychoeducation focused on the expected treatment effects. The patient understood that the treatment (if effective) would provide her with a window of opportunity to tackle her eating disorder and gain weight; she affirmed that she was motivated to overcome her AN. She also understood that, via application of metreleptin, her brain would lead her to think that starvation no longer applied and the door of the cage (AN) would be opened. Psychoeducation stressed the need to use the induced improvement to gain weight in order for her to increase her endogenous leptin secretion. She was requested to come up with a major symptom which bothered her and which she wanted to work on in small steps after discontinuation of dosing. At the end of the dosing period, the patient decided that she wanted to increase the number of ingested foods. To aid her in the achievement of this goal, weekday phone calls of 3–5 min were arranged for three weeks after cessation of dosing to allow the patient to name a novel food daily that she wished to reintroduce to her diet on the respective day. A follow-up examination was conducted 175 days after the completion of the dosing period.

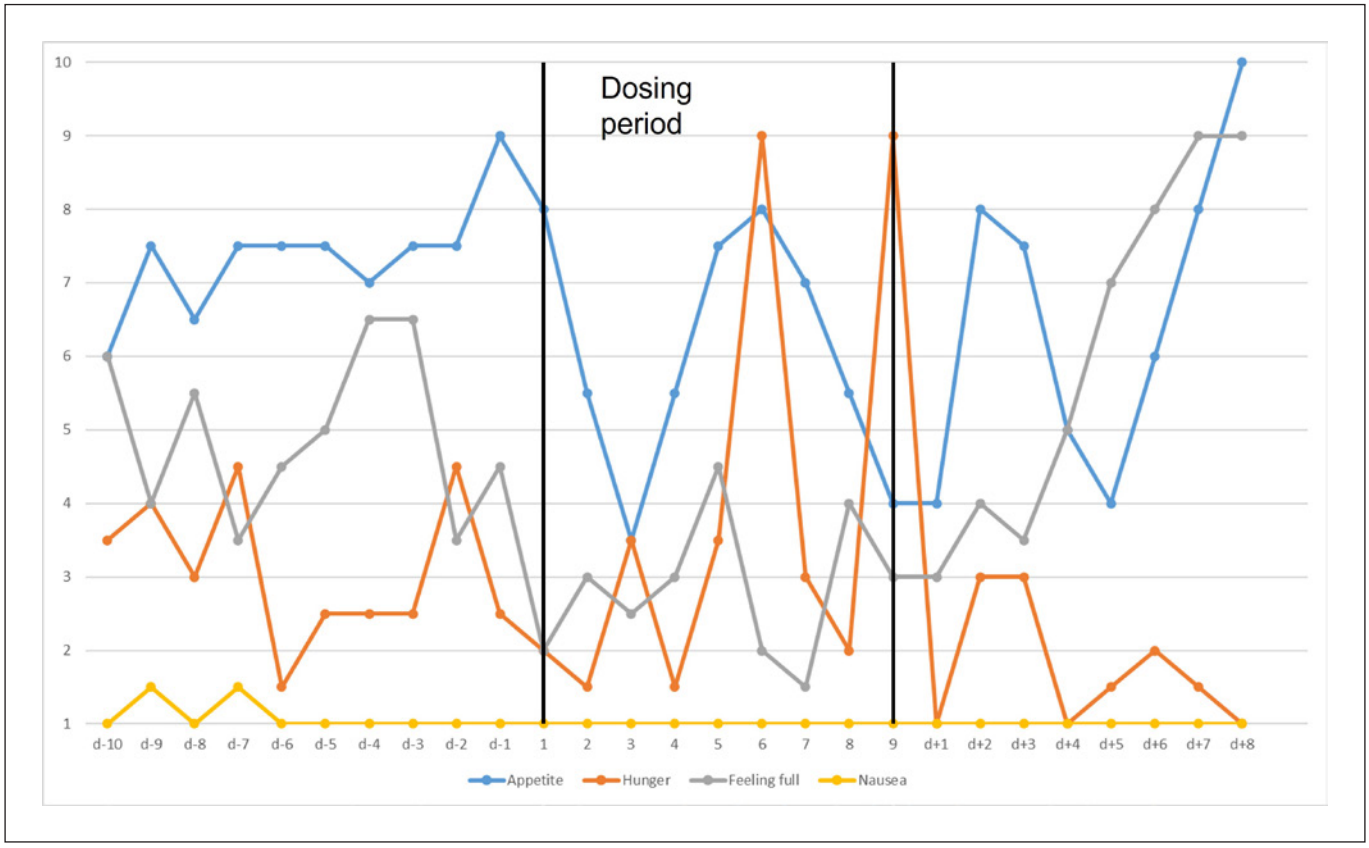

Fig. 3. Means of physiological parameters assessed twice daily with visual analogue scales (range 1–10) prior to, during, and after the 9-day dosing period.

Results

AN-associated key cognitions, inner tension, and depressed mood dropped within one to two days of treatment (Fig. 1, 2). The BDI-II score was halved (scores at d1 and d4, 27 and 13) on the fourth day of dosing; other items (e.g., interest in daily activities, interest in socializing) indicative of an antidepressant effect were ranked improved in the VAS (Fig. 3). Sleep quality improved, and the patient felt less tired and exhausted. Patient R also reported less mood swings and a reduced urge to harm herself (VAS, online suppl. Fig. 2). With the beginning of treatment, there was a marked drop in "feeling gripped by the disorder" and a surge of motivation for recovery (VAS self-rating). Apart from the patient, family members, and treatment staff described noticeably improved mood and higher vitality.

Rankings for appetite had been rather high prior to dosing (rankings between 6 and 9 in the 10 days prior to dosing) and showed substantial variation during the dosing period (3.5–8) with a peak of 10 occurring eight days into the post-dosing period. Hunger, which had been ranked between 1.5 and 4.5 prior to dosing, reached a peak value of 9 on dosing days six and nine (Fig. 3) to subsequently decline and reach the lowest value of 1 on threedays of the post-dosing period. Seemingly in parallel to the self-rankings for appetite and hunger, "feeling full" (Fig. 2) was rated lower during metreleptin dosing and increased thereafter. Binge eating was ranked low (maximal score of 3.5; online suppl. Fig. 3) prior to and during dosing but increased considerably in the post-dosage period. The urge to vomit was markedly reduced during dosing and increased afterwards (online suppl. Fig. 3). Towards the end of the dosing period, the patient's mother described patient R as more open to new types of food. Patient R also stopped cutting her food into tiny pieces, ate bread again for the first time in a year, and was able to imagine eating "forbidden foods".

Overall, the total raw score of the EDI-2 was remarkably lower on day four (online suppl. Table 1). Raw scores

for the subscales drive for thinness, ineffectiveness, and impulse regulation showed the greatest differences (online suppl. Table 1). Circulating leptin levels were within the starvation range (<2 ng/mL) prior to treatment and reached average levels (>50th percentile; endogenous leptin + metreleptin) under treatment (online suppl. Table 2).

In daily phone calls following discharge for three weeks, the patient described normal appetite and hunger with occasional food cravings in the afternoon and early evening and feelings of guilt, visible also in an increase in binge eating and the urge to vomit (VAS; online suppl. Fig. 3). She had, however, developed functional coping strategies (three main meals, three snacks). Patient R had agreed to the daily addition of new foods to her very limited menu and proudly reported her success in holding up her end of the agreement. She was also able to enjoy ice cream again and eat at a buffet. She had started her summer job and described herself as genuinely happy. Twenty days post-dosing, she had gained ten kg since her initial presentation (BMI 20.2 kg/m^2). The mother was struck by the normalized eating behaviour of her daughter (see supplement for a translation of an email sent to J.H.; d+52).

At the final follow-up (d+175), the patient had gained almost 20 kg since her first presentation (BMI 23.59 kg/m^2; 76th sex- and age-matched BMI-centile). She reported stable mood and fewer, intermittently occurring eating disorder cognitions (online suppl. Table 1). Menses returned three months post-treatment. The patient had resumed moderate physical activity and described healthy but normal eating habits. Binge eating stopped after the discontinuation of olanzapine treatment. BDI-II (score 13) and EDI-2 scores (online suppl. Table 1) were similar to those reported on day 4 of dosing. Leptin was in a low normal range (online suppl. Table 2). Patient R's mother remarked that treatment gave her back her friendly, happy, and amiable daughter.

Discussion

This case report recapitulates and extends previous observations made during metreleptin treatment of patients with AN [3, 4]. The improvements in mood (and related items) and eating disorder cognitions are again remarkable; the consistency of qualitative and quantitative aspects of the perceived changes renders expectation effects as an explanation highly unlikely (for a detailed discussion, see [3]). On the afternoon of dosing day three the patient reported that, during a walk, she perceived a substantial change in her experienced environment indicating that, despite improvements in ratings prior to dosing day 3, her perception of the improvement struck her rather abruptly. The intermittently high appetite and hunger ratings during the dosing period and the subsequent keenness of the patient to reintroduce previously "forbidden" foods along with the weight gain of 15 kg within six months are not compatible with the postulated anorexigenic effect of leptin. They also beg the question as to the mechanisms underlying the psychopathology and behaviour of patients with AN. In patient R, it appeared as if the short metreleptin dosing period of a mere nine days unleashed a process entailing rapid weight gain leading to a body weight compatible with that prior to development of AN (78th sex- and age-matched BMI-centile vs. 76th at the final follow-up). The "cage" was opened, and patient R was able and willing to make use of this opening.

It is currently unknown what serum concentration of metreleptin is required to induce the changes observed in patients with AN. We have previously used dosages of up to 11.3 mg [3], entailing jointly measured concentrations of endogenous leptin and metreleptin in the range of people with obesity and leptin resistance [28]. Currently, we do not know whether a bolus effect is required or whether a lower, but prolonged exposure to metreleptin is sufficient. Since off-label treatments focus solely on the benefit for the individual patient, systematic pharmacokinetic investigations need to be pursued in a RCT.

Based on the intermittent occurrence of high ratings of hunger during dosing and the post-dosing increase in appetite (Fig. 2), we postulate that the normalization/elevation of leptin signalling entails increased feelings of appetite and hunger via direct and/or indirect mechanisms. The initial development of the hypoleptinemia associated with AN might via direct central mechanisms reduce feelings of appetite/hunger or entail their reduced perception (in thus predisposed individuals), which can rapidly normalize upon restoration of normal leptin levels. Examples of indirect mechanisms include the strong and rapid-onset antidepressant effect, the reduction in inner tension, and/or a reduction in preoccupation with food and other eating disorder cognitions. Leptin is known to have effects on the gastrointestinal tract [29] which could also underlie or contribute to the observed increment of appetite/hunger. The decreased urge to vomit and the post-dosing increase in binge eating were seemingly also induced by metreleptin treatment. The patient reported a lessening of food cravings after she dis-

continued olanzapine upon day 150 after cessation of metreleptin treatment. Based on this observation, the frequent side effect of weight gain from this atypical neuroleptic seemingly also applied to patient R. Whereas olanzapine had no discernible effect on weight gain prior to metreleptin treatment, it may well have contributed to weight gain in the post-dosing period indicating a potential activation of this side effect.

In light of only a rather low percentage of patients with feelings of hunger during therapeutic fasting [20], it would be of obvious interest to see if metreleptin can also induce feelings of hunger and appetite in non-eating disordered individuals who undergo (therapeutic) fasting. Such an approach would allow an initial step towards disentangling direct from indirect effects of metreleptin in individuals with low leptin levels.

We hypothesize that metreleptin entails hunger and appetite, particularly in patients with AN who have a premorbid BMI in the upper age range. Thus, patient C [3] had had a high premorbid body weight of 92 kg. Patient F [4] had BMI values in the upper normal range during childhood. Patient R, too, had a premorbid BMI-centile of 78. Patient C was the only patient who expressed a certain ambivalence towards metreleptin treatment as a result of an increased appetite. It should be noted that patient C, in contrast to patient R, had received no prior information as to the possibility that appetite and hunger might increase as a consequence of metreleptin treatment. In the brief daily phone calls following the dosing period, it was amazing that R was readily willing to identify novel foods each day including, for instance, soft ice or choosing a food from a buffet. Patient R seemed to relish the possibility to increase the number of "allowed" foods in small steps; the rewarding effect of food was clearly discernible. Nevertheless, she experienced difficulties with food cravings and binge eating; fortunately, she did not develop bulimia nervosa or a binge eating disorder. Bulimia nervosa is an eating disorder that develops in 20–30% of patients with AN [30]. Single participants of the Minnesota Starvation Experiment had an overshooting weight gain and/or developed abnormal eating behaviour lasting up to several years after the end of the experiment [31, 32].

Hunger sets in upon a reduced caloric intake. Systematic data on ratings of appetite and hunger during starvation are few (see, for instance, Keys et al. [19]). Ethical considerations preclude a systematic investigation of the developmental course and inter-individual variation of such ratings upon transition into more severe degrees of starvation. Accordingly, it has been argued that the Minnesota Starvation Experiment is a case of unethical research and should thus not be cited [33]. We agree that this experiment would undoubtedly be perceived as unethical today; nevertheless, in light of the dire need to improve treatment of AN, we have cited this study to illustrate the overlapping symptomatology between AN and starvation unrelated to this eating disorder.

It appears possible that feelings of hunger may no longer persist upon medium term starvation, despite persistence of preoccupation with food, entailing a dissociation. It is speculative to consider the potential benefits of such a hormonally induced (other factors may act in concert) cessation of feelings of hunger. Guisinger [34] argued that distinctive symptoms of AN including food restriction, denial of starvation, and hyperactivity represent adaptive mechanisms that facilitated ancestral nomadic foragers leaving depleted environments. Genetically susceptible individuals who lose too much weight may trigger these archaic adaptations, which account for AN-like syndromes in both humans and animals. She suggests that AN may represent an adaptation to weight loss in itself.

In light of the female preponderance in AN, sex differences in regulation of leptin secretion during the manifestation period of this eating disorder warrant attention. Thus, plasma leptin levels increase in girls and decrease in boys after Tanner stage 2 as pubertal development proceeds [35]. Both a higher mean percent body fat and an increased synthesis of leptin per unit of fat mass explain the higher circulating leptin levels in females [36]. A reduced leptin secretion may predispose to AN [37]. AN typically manifests during the age period, in which leptin secretion changes substantially in females, potentially entailing a vulnerable period for derailment induced via weight loss.

In conclusion, our findings support the hypothesis that a substantial proportion of the symptomatology of AN results from leptin deficiency. We question the primary role of leptin as an anorexigenic hormone, particularly in individuals with hypoleptinemia. We hypothesize that leptin is the key hormone to trigger the adaptation to starvation; this adaptation includes both central and peripheral effects of leptin that may extend well beyond the established neuroendocrine adaptation via the hypothalamus-pituitary-end organ axes. Our results support the conception of AN as a metabo-psychiatric disorder [38], in which the hypoleptinemia-induced adaptation to starvation results in the entrapment in eating disorder specific cognitions, emotions, and behaviours. Clearly, clinical trials are warranted to substantiate these initial find-

ings and to determine the extent to which human recombinant leptin will impact the treatment of this eating disorder.

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Statement of Ethics

Both the patient and her mother (sole custody) provided written informed consent to participate in the study and to the publication of the case report. Due to German law ethics approval is not applicable for an off-label application of an otherwise approved drug in an individual patient.

Conflict of Interest Statement

Gertraud Gradl-Dietsch, Johannes Hebebrand (J.H.), and Jochen Antel (J.A.) declare that they will be named as inventors in a patent application that the University of Duisburg-Essen (UDE) prepares to file on the use of leptin analogues for the treatment of depression; J.H., J.A., and Gabriella Milos (G.M.) are also named as inventors in a patent application filed by the UDE for use of metreleptin in AN. Johannes Hebebrand received a speaker's honorarium from Amryt Pharmaceuticals in 2021. Martin Wabitsch has served as a consultant to Amryt Pharmaceuticals in 2020 and 2021. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

Gertraud Gradl-Dietsch, Johannes Hebebrand, and Jochen Antel all made substantial contributions to the conception of the work, data acquisition, analysis, and interpretation of data, as well as manuscript preparation, critical revision, and final approval. Gabriella Milos and Martin Wabitsch made substantial contributions to the conception of the work, interpretation of data, as well as manuscript preparation, critical revision, and final approval. Franziska Tschöpe and Rebecca Bell made substantial contributions to data acquisition and analysis, drafting of the work, and final approval.

Data Availability Statement

All directly sharable data are supplied with the supplementary material. Further enquiries can be directed to the corresponding author.

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