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Journal of Psychiatric Research 37 (2003) 165–169
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

# The effect of therapeutically induced weight gain on plasma leptin levels in patients with anorexia nervosa

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Received 15 July 2002; received in revised form 18 November 2002; accepted 22 November 2002

**Abstract**

Previously it was shown that hyperleptinemia ensues from the therapeutically induced weight gain in patients with anorexia nervosa (AN). However, not all studies have been able to confirm this finding. To further investigate leptin secretion during weight gain in AN and potential functional implications serum leptin levels, body mass index (BMI),% body fat, fT3, fT4 and TSH of 18 adolescent AN patients (BMI at admission: 14.4±1.2) were examined four times during 11 weeks of re-feeding and compared to 18 weight stable controls. Additionally, serum leptin levels, BMI and % body fat were determined in patients reaching target weight after 11–20 weeks (mean 14.3±3) of inpatient re-feeding. At admission patients showed lower lg10 leptin levels ($P=0.000$) and BMI ($P=0.000$) than controls. At target weight patients still had significantly lower BMI ($P=0.000$) and% body fat ($P=0.000$) than controls but lg10 leptin levels of patients were higher than those of controls when adjusted for BMI and% body fat (ANCOVA, group $P=0.038$). In patients, correlation coefficients between lg10 leptin levels and BMI increments increased during the 11 weeks of re-feeding. BMI,% body fat and fT3 levels were not significantly correlated to lg10 leptin levels in week 11, however, 53% of the variance of leptin levels (corrected $R^2=0.53$, $P=0.001$) was explained by BMI increments between weeks 7 and 11 ($P=0.001$) and lg10 leptin level at admission ($P=0.002$). In conclusion, we confirmed weight gain induced hyperleptinemia in AN. Further research is required to assess if this phenomenon contributes to renewed weight loss.


*Keywords:* Re-feeding; BMI; Relapse; Anorexia nervosa; Weight gain; Leptin

## 1. Introduction

Anorexia nervosa (AN) is a psychiatric disorder with a high mortality. Re-feeding therapies are efficient in weight rehabilitation but rates of short-term relapses are nevertheless high (Herpertz-Dahlmann et al., 2001). Whereas there is no evidence to support the occurrence of a specific disturbance of the leptin system in AN (Ferron et al., 1997; Hebebrand et al., 1995, 1997; Hinney et al., 1998) temporary adaptive changes of leptin concentrations possibly interfere with weight stabilisation during or shortly after re-feeding therapies. Hebebrand et al., (1997) and Mantzoros et al. (1997) found reduced concentrations of the adipocyte hormone leptin during the acute stage of AN and increased levels upon short-term weight restoration compared to age-matched normal-weight controls. In contrast, two studies reported on decreased serum leptin levels in anorectic patients after partial weight recovery in contrast to normal weight controls (Casanueva et al., 1997; Haluzik et al., 1999).

Leptin plays an important role in the hypothalamic regulation of food intake and energy homeostasis. In lean and obese humans (Heymsfield et al., 1999) and in genetically leptin-deficient obese and wild type animals (van Dijk, 2001) leptin administration leads to a loss of weight and fat. Weight loss is presumably promoted by

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0022-3956/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0022-3956(02)00100-0

a reduction of food intake, an increase in energy expenditure, thermogenesis and degradation of fat stores (van Dijk, 2001). Thus, it is tempting to hypothesise that elevated leptin levels in AN patients during re-feeding may be an important factor in the difficulties of reaching or maintaining target-weight (Hebebrand et al., 1997). The aim of this study was to confirm elevated leptin secretion upon weight gain and to attempt to identify factors contributing to transient hyperleptinemia in AN during re-feeding.

## 2. Materials and methods

Eighteen adolescent medication-free females with a DSM-IV diagnosis of AN and 18 normal-weight age-matched female controls were included in this study. Patients and their parents gave written informed consent for participation in the study, which was approved by the Ethics Committee of the University of Aachen. Diagnoses including AN subtype were based on the Structured Interview of Anorexia and Bulimia nervosa (SIAB; Fichter et al., 1998). Four patients were classified as binge eating/purging types and 14 as restricting subjects. Body impedance analysis (BIA) and BMI measurements were performed on the patients concomitantly with blood samplings after an overnight fast at 08:00 on day seven of the 1st (not BIA), 3rd, 7th and 11th week of re-feeding. Additionally, serum leptin levels, BMI and% body fat were determined in patients upon achievement of target weight. Controls were examined twice in a four week interval; at both examinations weight, height and body composition were investigated to rule out significant weight gain or loss; at the second examination blood samples were taken after an overnight fast at 08:00.

A body weight corresponding to the 25th age- and sex-specific BMI-percentile was defined as the target weight (Guidelines of the German Scientific Society for Child and Adolescent Psychiatry and Psychotherapy, 2000). Body composition was determined by a four-frequency body impedance analysis device (BIA, Data Input, BIA 2000-M, Software Nutri 4, Hofheim, Germany). BIA was not performed in week 1 because during re-hydration that mainly takes place in the first week of re-feeding, impedance data are not reliable (Birmingham et al., 1996). fT3, fT4 and TSH were measured by chemiluminiscence (ACS Centaur, Chiron Diagnostics, Fernwald, Germany; intra-assay variance: fT3 2.78%; fT4 3.1%; TSH 2.33%; inter-assay variance: fT3 3.71%; fT4 2.71%; TSH 3.6%). Leptin was measured with a sensitive RIA (Human-Leptin-RIA sensitive, Mediagnost, Tübingen, Germany; intra-assay variance $<5\%$; inter-assay variance $<7.6\%$).

Mean values of biological parameters in the patients' group and in controls (second measurement) were compared by Student's t-test. The Spearman rank order correlation coefficient was used to examine the relationship between different parameters. The change of parameters during 11 weeks of inpatient treatment was analysed by a repeated-measurement ANOVA. The partial rank order correlation was used to control for the effect of BMI on the correlation between fT3 and lg10 leptin. Univariate covariance analysis (ANCOVA) was used to determine if leptin levels were different between patients at target weight and controls when adjusted for BMI and% body fat. Multiple linear regression analysis (stepwise backward procedure) was used to examine the relationship between leptin levels in week 11 and possible prediction variables (BMI in week 1 and 11, leptin level in week 1, BMI increment ($\Delta$ BMI) between weeks 7 and 11. Logarithmic (lg10) transformation was performed for leptin data to avoid asymmetrical distribution .

Significance was defined as $P \leqslant 0{,}05$. Data are presented as mean$\pm$S.D. Statistic calculation was performed using SPSS-99 software.

## 3. Results

In week 1 patients and controls did not differ significantly in age (AN: $14.1\pm1.2$ years; controls: $13.9\pm0.8$ years; n.s.) and height (AN: $167\pm1$ cm; controls: $163\pm1$ cm; n.s.). In contrast, weight (AN: $39\pm5.3$ kg; controls: $55\pm7.5$ kg; $P=0.000$) and BMI (AN: $14.4\pm1.2$ kg/m$^2$; controls: $20.8\pm1.9$ kg/m$^2$; $P=0.000$) differed significantly. From week 1 to week 11 weight increased by $0.72\pm2.2$ kg/week in the patient group. Patients reached target weight after 11–20 weeks of inpatient re-feeding (mean $14.3\pm3$ weeks). BMI,% body fat, leptin and fT3 levels significantly increased during re-feeding (Table 1). Levels of fT4 and TSH did not change significantly during re-feeding and were within the respective reference range (fT4: 10.1–19.0 pmol/l; TSH: 0.35–5 mU/l) at all measurements in patients and controls. In the control group BMI and% body fat did not change significantly between the first and second measurement (Table 1).

*T*-tests revealed that compared to controls patients' BMI and% body fat were significantly lower at all time points ($P=0.000$); levels of fT3 were significantly lower from week 1 ($P=0.000$) to week 11 ($P=0.03$), in week 1 patients had lg10 leptin levels well below the controls ($P=0.000$) but not in week 11 ($P=0.559$) and at target weight ($P=0.397$). ANCOVA revealed that compared to controls lg10 leptin levels were higher in patients at target weight (group: $P=0.038$) but not in week 11 (group: $P=0.137$) when adjusted for BMI and% body fat. Fig. 1 illustrates that lg10 leptin concentrations of 17 of 18 patients at target weight lie above the regression line generated from analysis of the control group.