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ORIGINAL CONTRIBUTION

Lower serum leptin levels in female students of the nutritional sciences with eating disorders

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Summary *Background* Evidence has accumulated that in both acutely ill and recovered patients with either anorexia or bulimia nervosa circulating leptin levels (LL) are lower than in controls matched for body mass index (BMI; kg/m^2). It is unknown if these lower leptin levels represent a state or trait marker. *Aim of the study* We aimed to confirm the lowered leptin levels in eating disordered females and to identify underlying mechanisms. *Methods* We screened 181 female students of the nutritional sciences for eating disorders with the respective module of the M-Composite International Diagnostic Interview and the Cognitive Restraint scale of the Three Factor Eating Questionnaire. The physical assessment included determinations of BMI, body composition and LL. Each case fulfilling lifetime DSM-IV criteria for an eating disorder was BMI matched to two controls. We used a multivariate mixed regression model to evaluate if the observed difference in lg_{10}-leptin level between cases and controls is actually due to the influence of restrained eating and/or previous weight loss after adjustment for BMI and percent body fat. *Results* In accordance with our hypothesis the 32 (17.7 %) cases had a lower serum lg_{10}-leptin level than the 64 BMI matched controls (one-sided $p < 0.001$). We were not able to detect an influence of restrained eating or previous weight loss. *Conclusions* We confirm that females with a lifetime history of an eating disorder have lower LL. We were not able to identify an underlying mechanism. Similar to most previous studies we found a high rate of eating disorders among female students of nutritional sciences.

Key words anorexia nervosa – bulimia nervosa – leptin levels – dietetics – restrained eating – weight loss

Introduction

Leptin is a hormone that is secreted into the bloodstream mainly by adipocytes [1]. Serum levels of this hormone are highly correlated with body mass index (BMI; kg/m^2) and percent body fat (%BF; 2). Short-term fasting, short-term and prolonged weight loss and hypercaloric dieting lead to disproportionate drops and increments, respectively, of circulating leptin levels (LL) [3–5], indicating a dynamic regulation superimposed on the dependency on fat mass. Leptin receptors can be detected in the hypothalamus and in several other brain regions [6, 7]. The neural circuits that are downstream of leptin receptors influence leptin's endocrine, autonomic and behavioral effects [8, 9].

One of leptin's major functions is to adapt the organism to semistarvation via downregulation of the hypothalamic-pituary-gonadal and hypothalamic-pituary-thyroid axes and upregulation of the hypothalamic-

pituary-adrenal axis [10, 11]. Accordingly, in patients with anorexia nervosa (AN) LL are well below age-matched controls [12–17] and presumably contribute to the reduced gonadotropin secretion characteristic of this eating disorder [18–22]. Nevertheless, similar to findings in healthy individuals, LL are correlated with both BMI and %BF in the acute stage of AN [13, 14, 23–25].

A correlation between BMI and LL has also repeatedly been demonstrated in patients with bulimia nervosa (BN) and in mixed study groups encompassing females with AN and BN, respectively [15, 16, 18, 26–29]. Recent evidence indicates that LL in patients with acute BN and in patients stably recovered from BN have lower LL than expected for BMI [26–29] and %BF [28]. Other reports have indicated that in both acutely ill and long term recovered patients with AN LL are also lower than in BMI matched controls [13, 30].

In the current study we test the hypothesis that females with a lifetime history of an eating disorder have lower LL than controls using a case-control design. To ascertain cases and controls matched for BMI we screened a study group of 181 students of nutritional sciences for the lifetime occurrence of any DSM-IV eating disorder. The choice of students of nutritional sciences was motivated by previous studies amongst students of dietetics or nutritional sciences [31–35], which had revealed elevated rates of disordered eating behavior. If the initial hypothesis is substantiated, we use a multivariate mixed regression model to evaluate if the observed difference in LL between cases and controls is actually due to the influence of specific variables, for which we have *a priori* hypotheses as to their influence on LL.

Subjects, materials and methods

181 female students of the nutritional sciences of the University of Gießen were ascertained in 1998 via use of advertisements within the Institute of Nutritional Sciences. The Ethics Committees of both the Medical Faculties of the Universities of Marburg and Gießen had approved the study. All probands gave written informed consent.

The students were interviewed using the standardized eating disorders module of the M-Composite International Diagnostic Interview (M-CIDI; 36), which addresses the criteria for each eating disorder one by one. The M-CIDI is a reliable screening tool used to identify psychiatric disorders (36a, 36b). Additionally, we used structured questions to assess past and current intake of hormonal contraceptives and history of menstrual disorders. A lifetime diagnosis of AN, BN, Eating Disorders Not Otherwise Specified (EDNOS) or a Binge eating disorder (BED), repectively applied if the respective DSM-IV criteria were met.

Weights and heights were measured using calibrated instruments. 1.5 kg was subtracted from measured weights to account for light clothing. Individual BMI centiles based on the German National Nutrition Survey were determined as described previously [37].

Bioelectrical impedance measurements (BIA, 2000-S; Data Input GmbH, Frankfurt) and blood sampling were performed after an overnight fast. %BF was calculated from measured resistance using Deurenberg's gender specific equations for individuals aged ≥ 16 years. Fat free mass (FFM) predicted by Deurenberg's equations differs only slightly from FFM measured densitometrically in individuals whose BMIs are ≤ 35 kg/m^2 [40]. Serum leptin levels were measured with a sensitive RIA [13, 41]. Inter- and intra-assay coefficients of variation are 8.5 and 0.8 %, respectively.

Every student who received a diagnosis of any eating disorder (case), was BMI-matched to two students without an eating disorder (controls). This matching procedure led to BMI differences between cases and controls of between 0.0 and 0.38 kg/m^2 with 3 exceptions: For a case with a BMI of 21.0 kg/m^2 the closest match for the second control had a BMI of 19.6 kg/m^2. A case with a BMI of 32.2 kg/m^2 was matched to two controls with BMI of 29.9 and 29.6 kg/m^2, respectively. These imperfect matchings were conservative in the sense that the higher BMI in these cases cannot contribute to their hypothesized lower LL.

All students were asked to recall their maximal weight during adulthood (age ≥ 18 years) to allow calculation of the maximal BMI based on currently measured height. The difference between this maximal and current BMI was taken as a crude measure of net weight loss during adulthood. Because three students self-reported their maximal weights below current measured weights, we set the resulting BMI difference of –1.29, –0.03 and 0.01 kg/m^2, respectively, to 0. The probands were also asked for recalled body weights one, three, and 12 months prior to the current assessment. All students filled in the Three Factor Eating Questionnaire (TFEQ; 38, 39).

Means, standard deviations of the mean and ranges of all variables and the score of the Cognitive Restraint scale of the TFEQ for the whole study group are illustrated in Table 1.

Statistics

We use a hierarchical test procedure: We initially test the hypothesis that the n students who fulfill lifetime criteria for any eating disorder (cases) have lower leptin levels than the 2n BMI matched controls. For this purpose lg_{10}-LL of individual cases are compared to the mean lg_{10}-LL of the respective two controls using the t-test for paired samples. In the case of a significant difference in

Table 1 Description of the total study group screened (n = 181)

Variable	Total study group (n = 181) mean (sd/range)
Age (years)	23.6 (2.93/19–36)
Weight (kg)	61.8 (9.75/42.4–117.4)
BMI (kg/m^2)	21.1 (2.94/14.7–39.7)
BMI-Percentile	46.2 (27.99/0–100)
Fat mass (kg)	20.1 (5.87/9–57.8)
Percent body fat	32.8 (4.18/20.8–49.9)
Maximal BMI	22.4 (3.30/15.5–41)
Cognitive Restraint scale score	7.6 (4.82/0–21)
Leptin (µg/l)	12.2 (8.76/0.5–59.4)

lg_{10}-LL we examine the influence of four quantitative variables performing a mixed model analysis of variance including the matching group status (n trios each consisting of 1 case and 2 controls) as a random effect.

The independent variables include BMI, % body fat (%BF), the difference between maximal and current BMI and the score of the Cognitive Restraint scale of the TFEQ: BMI and %BF are of obvious interest in the light of their known correlation with LL [2]. Because weight loss has been shown to result in a disproportionate decrease in LL [3], we include the difference between maximal lifetime BMI in adulthood and current BMI as an indicator for net weight loss during adulthood. Finally, due to the previous detection of lower LL adjusted for %BF in underweight females with a restrained eating behavior [42], we additionally evaluate the influence of the score of the Cognitive Restraint scale of the Three Factor Eating Questionnaire [38].

We had additionally hypothesized that recent weight gain or loss has an influence on LL. In order to assess recent weight change we calculated the differences between current and recent BMI (1, 3 and 12 months ago). Unfortunately, the inclusion of these parameters led to substantial decreases in sample size up to 40 % (14 out of 32 trios) due to missing values; the probands were unable to recall their respective past weight(s). Because these missings are possibly non-random, we do not report the respective results. Instead, we refer to these analyses in a cursory fashion in the Discussion. Because of the similarly small age range amongst cases and controls (for both groups combined the 5th and 95th age centiles were 20.3 and 28.1 years; mean ages were 22.99 vs 23.50 years, respectively, p = 0.31) we refrained from including age in the model.

For descriptive purposes we refer to the absolute values of LL and use the normally distributed lg_{10}-LL for the statistical analyses.

Results

32 (17.7 %) of the 181 students met lifetime criteria for any eating disorder. AN proved to be the most common eating disorder (n = 13; 7.2 %); six and seven students had the restricting and binge eating/purging type, respectively. Among the six (3.3 %) students with BN four had the purging type, two the non-purging type. EDNOS were diagnosed in 13 (7.2 %) females and included three students with atypical AN, eight students with atypical BN and two females with BED.

The comparison of lg_{10}-LL between the 32 cases and the 64 BMI matched controls substantiated our hypothesis (Table 2): The respective 95 % confidence intervals of LL do not overlap (cases: 6.19–11.23 µg/L, controls: 11.49–14.35 µg/L); lg_{10}-LL differed significantly (one sided $p < 0.001$).

On a descriptive basis, the subdifferentiation according to the kind of eating disorder diagnosed with the M-CIDI showed that irrespective of the diagnosis lg_{10}-LL were consistently lower in cases than controls (see Table 2). lg_{10}-LL differed most between cases with AN and their corresponding controls (one sided $p = 0.001$). 6 subjects with a lifetime diagnosis of BN showed a trend towards lower lg_{10}-LL compared to their 12 controls (one sided $p < 0.1$).

On a descriptive basis, no difference in fat mass (or %BF) was apparent (Table 2). Compared to their 64 controls the 32 cases had higher mean maximal BMIs (one-sided $p < 0.05$), higher scores of the Cognitive Restraint scale of the TFEQ (one sided $p < 0.001$) and in addition, their net weight loss during adulthood was also higher (one-sided $p = 0.026$) (Tabel 2).

The Analysis of variance (Table 3) revealed that percent body fat explains variation of lg_{10}-LL while BMI had no further effect. Neither the Restraint score nor net weight loss during adulthood had an effect on lg_{10}-LL. However, about 30 % of lg_{10}-LL's variance is explained by the case-control status i. e. due to unobserved physiological mechanisms. The whole model explained 66 % of the variance of lg_{10}-LL ($p < 0.001$).

Discussion

We substantiated our initial hypothesis: Students with a lifetime eating disorder had significantly lower LL than BMI matched controls. This result is well in line with previous findings of lowered LL in acutely ill and recovered patients with AN and BN [13, 26–30]. In our study, however, cases were not identified via a patient status; instead, the 32 cases formed a subgroup among 181 female students of nutritional sciences who were screened for eating disorders using the respective module of the M-CIDI (36a).

A total of 32 (17.7 %) of the participating students

Table 2 Descriptive comparison of somatic data and the scores of the Cognitive Restraint Scale (Stunkard and Messnick, 1985) between BMI-matched students with (n = 32; cases) and without (n = 64; controls) a lifetime eating disorder

	All Eating Disorders Combined		Anorexia nervosa		Bulimia nervosa		Atypical AN		Atypical BN		Binge-Eating Disorder	
	Cases n = 32	Controls n = 64	Cases n = 13	Controls n = 26	Cases n = 6	Controls n = 12	Cases Cn = 3	Controls n = 6	Cases n = 8	Controls n = 16	Cases n = 2	Controls n = 4
	Mean (standard deviation)											
Weight (kg)	61.6 (10.95)	59.5 (9.07)	58.8 (10.60)	57.8 (9.52)	72.9 (14.69)	67.3 (9.42)	58.4 (4.48)	54.2 (4.50)	61.1 (4.58)	60.0 (6.35)	51.8 (0.78)	53.3 (5.86
BMI (kg/m^2)	20.9 (3.02)	20.8 (2.73)	20.0 (2.69)	20.1 (2.63)	24.1 (4.25)	23.7 (3.18)	19.3 (0.73)	19.3 (0.63)	21.1 (1.37)	21.0 (1.44)	18.4 (0.42)	18.4 (0.53)
Fat mass (kg)	20.2 (6.47)	19.6 (5.09)	18.5 (5.45)	18.5 (4.98)	27.0 (10.04)	24.3 (6.28)	17.8 (2.09)	16.9 (1.30)	20.1 (2.61)	19.8 (3.14)	15.4 (0.67)	15.4 (2.30)
% body fat	32.2 (3.93)	32.5 (3.81	30.9 (3.37)	31.6 (3.69)	36.1 (5.65)	35.7 (4.62)	30.4 (1.44)	31.2 (0.63)	32.7 (2.39)	32.9 (2.86)	29.7 (0.85)	28.7 (1.18)
Maximal BMI (kg/m^2)	22.8 (3.78)	22.0 (3.05)	22.4 (4.39)	21.1 (2.95)	26.7 (3.17)	25.1 (3.72)	19.6 (1.45)	20.5 (1.37)	22.7 (1.63)	22.1 (1.44)	20.4 (0.48)	19.2 (0.69)
Δ BMI	0.006	0.24	0.22	0.38	0.57	–0.27	0.35	0.42	–0.57	0.28	–0.49	0.95
Curr. – 3 mo. ago	1.57	0.86	(1.53)	0.57	0.56	1.18	1.31	0.36	2.33	0.58	0.37	1.87
Cognitive Restraint score	11.3 (4.52)	6.2 (4.13)	13.0 (4.51)	5.4 (4.24)	10.2 (4.76)	6.3 (3.17)	12.3 (4.62)	6.7 (5.54)	10.4 (3.42)	8.0 (4.10)	5.0 (4.24)	3.5 (1.73)
Leptin (ng/ml)	8.7 (7.28)	12.0 (7.07)	5.7 (2.85)	10.0 (5.61)	15.1 (13.46)	18.5 (9.18)	8.2 (6.61)	9.3 (3.01)	9.4 (4.75)	11.9 (6.62)	7.1 (4.38)	9.2 (3.81)

Table 3 Multivariate regression model for explanation of variance of log_{10} serum leptin levels by group and case control status, BMI, percent body fat, difference between maximal BMI in adulthood and current BMI (delta BMI) and score of the Cognitive Restraint scale. The model explains 65.7 % of the variance of lg_{10} leptin level ($p < 0.0001$)

Variable	Analysis of variance				Regression model	
	SS	df	mean square	Pr > F	Estimate	Pr > |t|
Intercept					–0.153	0.51
Group status	1.25933	31	0.04062	0.55	/	
Case control status	0.29125	1	0.29125	0.01	–0.155	0.01
BMI	0.01928	1	0.01928	0.50	0.062	0.50
Δ BMI	0.04624	1	0.04624	0.30	–0.020	0.30
Cognitive restraint score	0.00436	1	0.00436	0.75	0.002	0.75
% body fat	0.25016	1	0.25016	0.02	0.033	0.02

SS sum of squares; *df* degrees of freedom; *Pr > F* probability derived from the F-distribution; *Estimate(s)* α- and β-coefficients, respectively; *Δ BMI* difference between current and maximal BMI during adulthood

fulfilled criteria for AN, BN or EDNOS. This high rate is in line with the majority [31–35, 43], but not all [44, 45] previous studies amongst students of dietetics, students of nutritional sciences or amongst those who have completed their education. The gender ratio among these students is approximately 9:1 for females and males. We cannot exclude that our ascertainment procedure possibly led to or contributed to the high rate of eating disorders by selection-biased enrollment. Obviously, we cannot compare the observed rate of eating disorders with other student populations for lack of such a control group. Nevertheless, the high rate found here appears quite alarming. It should be noted that our study is the first to interview students with a standardized module for eating disorders. In the aforementioned studies, only questionnaires were used to assess the frequency of disordered eating behavior in patients. In addition, our study represents the first that combines an interview with a physical assessment including blood sampling for determination of LL.

An issue of concern is whether all interviewed students indeed admitted to (or realized) having symptoms of an eating disorder. Because cases had lower lg_{10}-LL than the BMI-matched controls we are confident that the students identified as cases indeed differed from the controls. However, we cannot exclude that some of the controls dissimulated past or present symptoms of an eating disorder or were unaware of them. The female student with both the lowest BMI and LL (14.67 kg/m^2; 0.54 μg/L) serves to illustrate this aspect: Whereas we

have little doubt that this student had AN, she did not fulfill the DSM-IV criteria for any eating disorder upon completion of the interview. Furthermore, although not having assessed this aspect systematically we had the impression that some of the cases did not know that they had (had) an eating disorder.

Based on these observations we think that the identified rate of 17.7 % might actually even underestimate the real lifetime prevalence of eating disorders among this student group. On the other hand, we cannot totally exclude that the advertisement for the study induced students with abnormal eating behavior to preferentially participate. Such students might have perceived the study as a means to seek help; indeed, two students with an eating disorder contacted the senior author to obtain information as to therapeutic options within days after the assessment procedure. Irrespective of these considerations, we believe that within the curricula of students of nutritional sciences eating disorders should be dealt with extensively.

A drawback of our study is that we are not reliably able to distinguish current from past eating disorders. Whereas the M-CIDI attempts to distinguish past from current AN and BN by asking if dieting behavior and binge eating attacks, respectively, persist, we refrained from categorizing our cases accordingly. Thus, as required in the M-CIDI, ongoing dieting behavior is by no means sufficient to conclude that a diagnosis of AN still applies; similarly, a recent history of binge eating attacks is by itself insufficient to diagnose current BN. However, it is of interest to point out that those 13 cases, who fulfilled lifetime criteria for AN had a mean BMI of 20.04 kg/m^2 (Table 2), which is well above that required for a diagnosis of this eating disorder. Only two of these cases had a current BMI < 17.5 kg/m^2 (16.5 and 17.4 kg/m^2), revealing that the majority no longer fulfilled the diagnostic criteria for AN.

The particularly low mean LL among these AN cases again indirectly validates the diagnostic procedure. Furthermore, 6 cases that fulfilled lifetime criteria for BN (Table 2) had a BMI well above those with either AN, EDNOS or the whole study group (Table 1). Similarly aged females with BN identified in a community sample [46] or as inpatients [47] have previously also been shown to have a mean BMI in the same range as our BN cases.

Interestingly, no differences in fat mass (or %BF) were apparent between cases and controls (Table 2). This result is in line with a study of both acutely ill and recovered BN patients [27, 28], whose BMI and %BF were not responsible for the observed reduction in LL. In long term recovered AN patients we had previously found a trend towards lower LL as compared to BMI matched controls ($p = 0.051$); however, in contrast to the current study, %BF had differed between cases and controls ($p = 0.01$; 30). We had assumed that the former patients, who had been followed-up 10 years after admission for inpatient treatment, were more physically active than the BMI matched controls, thus explaining their higher fat free mass. In the current study %BF and fat mass were similar between cases and controls irrespective of the type of eating disorder (Table 2).

Basically, lower leptin levels in eating disordered cases as compared to BMI matched controls can reflect both a state and trait marker. In order to identify potential mechanisms underlying the lower leptin levels in cases as compared to controls we included five variables within our mixed model analysis of variance. Whereas many more variables might potentially influence LL, we restricted our study to those variables for which we were able to state clear hypotheses as to their influence on LL. In contrast to our expectation, neither net weight loss (defined as the maximal adult BMI minus the current BMI) nor the score of the Cognitive Restraint score predicted lg_{10}-LL (respective p-values > 0.05). The effect of %BF was no surprise in the light of the well known relationship between this variable and LL; the BMI did not independently explain additional variance. The fact that the case-control status still predicted LL indicates that the other variables were not sufficient to explain the lower LL in cases.

Unfortunately, we were not able to estimate the effect of recent weight change. Whereas we had asked all probands to recall body weights one, three and 12 months prior to assessment, a substantial subgroup was not able to recall one or more of these weights, thus implying a high number of potentially non-random missings. In our post-hoc analyses based on sample sizes reduced by as much as 40 % we found evidence for a substantial influence of recent weight history on LL. Based on these preliminary findings future studies should include respective parameters as potentially relevant variables; appropriate efforts should be undertaken to minimize the number of missing values. Alternatively, and more appropriately, we recommend a prospective approach.

In our opinion, three major aspects should be considered for an adequate interpretation of our regression model:

1) In the light of the low number of female students with AN, BN or EDNOS, respectively, we decided to treat all individuals irrespective of their eating disorder as one group. Undoubtedly, subgroupings based on the type of eating disorder would appear more appropriate, if a sufficiently high number of cases can be ascertained. However, the fact that lower LL were detected in all subgroups (Table 2), suggests a common underlying mechanism.
2) As we had expected, the score of the Cognitive Restraint scale is higher in cases than controls (Table 2). This difference is not surprising in the light of previous studies revealing high Restraint scores in eating disordered patients [48, 49]; furthermore, abnormal

eating patterns including restrained eating are known to persist in patients even after recovery [50]. However, and in contrast to our previous study in underweight students [42] the Cognitive Restraint scale score did not explain variance in lg_{10}-LL. Obviously, in the current study the cases were mostly not underweight (Table 2). It could very well be that only the high scores in cases do indeed reflect a restrained eating behavior with a biological correlate in the form of lowered LL. Controls might score high on the scale, but simply do not have an eating behavior consistent with their ratings.

3) Previously, only recent weight loss has been shown to result in a disproportionate decrease in LL [2]. We are not aware of a study that has addressed a medium or long-term effect of weight loss on LL. In our study, we were not able to address temporal aspects related to the assumed weight loss. Perhaps only recent weight loss is associated with lower leptin levels.

In this context it seems to be worth mentioning that rats set on dieting increase their physical activity while their serum leptin decreases to very low levels. This observation seems to be paralleled by eating disordered, especially by anorectic patients who often show hyperactivity, low LL and low body weight [51]. Further efforts will be necessary to clear the physiological complexity of this issue.

In conclusion, our results further support the notion that measurement of LL represents a means of validating the disordered eating behavior associated with eating disorders. Further research is required to address whether reduced LL represent a state or trait marker for eating disorders.

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References

1. Halaas JL, Gajiwala KS, Maffei M, et al. (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. Science 28:543–546
2. Considine RV, Sinha MK, Heiman ML, et al. (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. New Engl J Med 334: 292–295
3. Kolaczynski JW, Considine RV, Ohannesian J, Marco CC, et al. (1996a) Responses of leptin to short-term fasting and refeeding in humans: a link with ketogenesis but not ketones themselves. Diabetes 45:1511–1515
4. Kolaczynski JW, Ohannesian JP, Considine RV, Marco CC, Caro JF (1996b) Response of leptin to short-term and prolonged overfeeding in humans. J Clin Endocr Metab 81:4162–4165
5. Wadden TA, Considine RV, Foster GD, Anderson DA, Sarwer DB, Caro JS (1997) Short- and long-term changes in serum leptin in dieting obese women: Effects of caloric restriction and weight loss. J Clin Endocr Metab 83:214–218
6. Couce ME, Burguera B, Parisi JE, Jensen MD, Lloyd RV (1997) Localization of leptin receptor in the human brain. Neuroendocrinology 66:145–150
7. Elmquist JK, Ahima RS, Elias CF, Flier JS, Saper CB (1998b) Leptin activates distinct projections from the dorsomedial and ventromedial hypothalamic nuclei. Proceedings of the National Academy of Sciences of the United States of America 20:741–746
8. Halaas JL, Friedman JM (1997) Leptin and its receptor. J Endocrinol 155: 215–216
9. Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395:763–770
10. Ahima RS, Prabakaran D, Mantzoros C, et al. (1996) Role of leptin in the neuroendocrine response to fasting. Nature 382:250–252
11. Ahima RS, Flier JS (2000) Leptin. Annu Rev Physiol 62:413–437
12. Hebebrand J, van der Heyden J, Devos R, et al. (1995) Plasma concentrations of obese protein in anorexia nervosa. Lancet 346:1624–1625
13. Hebebrand J, Blum WF, Barth N, et al. (1997) Leptin synthesis in patients with anorexia nervosa is reduced in the acute stage and elevated upon short-term weight restoration. Mol Psychiatry 2:330–334
14. Grinspoon S, Gulick T, Askari H, et al. (1996) Serum leptin levels in women with anorexia nervosa. J Clin Endocr Metab 81:3861–3863
15. Ferron F, Considine RV, Peino R, Lado IG, Dieguez C, Casanueva FF (1997) Serum leptin concentrations in patients with anorexia nervosa, bulimia nervosa and non-specific eating disorders correlate with the body mass index but are independent of the respective disease. Clin Endocrinol 46:289–293
16. Argente J, Barrios V, Chowen JA, Sinha MK, Considine RV (1997) Leptin plasma levels in healthy Spanish children and adolescents, children with obesity, and adolescents with anorexia nervosa and bulimia nervosa. J Pediatr 31:833–838
17. Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC (1997) Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. J Clin Endocr Metab 82: 1845–1851
18. Köpp W, Blum WF, von Prittwitz S, et al. (1997) Low leptin levels predict amenorrhea in underweight and eating disordered females. Mol Psychiatry 2: 335–340
19. Ballauff A, Ziegler A, Emons G, et al. (1999) Serum leptin and gonadotropin levels in patients with anorexia nervosa during weight gain. Mol Psychiatry 4: 71–75
20. Warren MP, Voussoughian F, Geer EB, Hyle EP, Adberg CL, Ramos RH (1999) Functional hypothalamic amenorrhea: hypoleptinemia and disordered eating. J Clin Endocr Metab 84:873–877
21. Mantzoros CS (2000) Role of leptin in reproduction. Ann N Y Acad Sci 900: 174–183
22. Wabitsch M, Ballauff A, Holl R, et al. (2001) Serum leptin, gonadotropin, and testosterone concentrations in male patients with anorexia nervosa during weight gain. J Clin Endocr Metab 86: 2982–2988
23. Eckert ED, Pomeroy C, Raymond N, Kohler PF, Thuras P, Bowers CY (1998) Leptin in anorexia nervosa. J Clin Endocr Metab 83:791–805
24. Mathiak K, Gowin W, Hebebrand J, et al. (1999) Serum leptin levels, body fat deposition, and weight in females with anorexia or bulimia nervosa. Horm Metab Res 31:274–277

25. Balligand JL, Brichard SM, Brichard V, Desager JP, Lambert M (1998) Hypoleptinemia in patients with anorexia nervosa: loss of circadian rhythm and unresponsiveness to short-term refeeding. Eur J Endocrinol 138:415–420
26. Monteleone P, Bortolotti F, Fabrazzo M, La Rocca A, Fuschino A, Maj M (2000) Plasma leptin response to acute fasting and refeeding in untreated women with bulimia nervosa. J Clin Endocr Metab 85:2499–2503
27. Brewerton TD, Lesem MD, Kennedy A, Garvey WT (2000) Reduced plasma leptin concentrations in bulimia nervosa. Psychoneuroendocrino 25:649–658
28. Jimerson DC, Mantzoros C, Wolfe BE, Metzger ED (2000) Decreased serum leptin in bulimia nervosa. J Clin Endocr Metab 85:4511–4514
29. Baranowska B, Wolinska-Witort E, Wasilewska-Dziubinska E, Roguski K, Chmielowska M (2001) Plasma leptin, neuropeptide Y (NPY) and galanin concentrations in bulimia nervosa and in anorexia nervosa. Neuroendocrinol Lett 22:356–358
30. Frey J, Hebebrand J, Müller B, et al. (2000) Reduced body fat in long-term followed-up female patients with anorexia nervosa. J Psychiat Res 34: 83–88
31. Crockett SJ, Littrell JM (1985) Comparison of eating patterns between dietetic and other college students. J Nutr Educ 2:47–50
32. Drake MA (1989) Symptoms of anorexia nervosa in female university dietetic majors. J Am Diet Assoc 89: 97–98
33. Fredenberg JP, Berglund PT, Dieken HA (1996) Incidence of eating disorders among selected female university students. J Am Diet Assoc 96:64–65
34. Reinstein N, Koszewski WM, Chamberlin B, Smith-Johnson C (1992) Prevalence of eating disorders among dietetics students: does nutrition education make a difference? J Am Diet Assoc 92: 949–953
35. Howat PM, Beplay S, Wozniak P (1993) Comparison of bulimic behavior incidence by profession: dietitian, nurse, teacher. J Nutr Educ 25:67–69
36. a) Wittchen HU, Lachner G, Wunderlich U, Pfister H (1998) Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). Soc Psychiatry Psychiatr Epidemiol 33: 568–578
b) Wittchen HU, Nelson CB, Lachner G (1998) Prevalence of mental disorders and psychosocial impairments in adolescents and young adults. Psychol Med 28:109–126
37. Hebebrand J, Himmelmann GW, Heseker H, Schafer H, Remschmidt H (1996) Use of percentiles for the body mass index in anorexia nervosa: diagnostic, epidemiological, and therapeutic considerations. Int J Eat Disord 19: 359–369
38. Stunkard AJ, Messick S (1985) The Three Factor Eating Questionnaire to measure dietary restraint, disinhibition and hunger. Journal Psychosom Res 29: 71–83
39. Pudel V, Westenhöfer J (1989) Fragebogen zum Eßverhalten: Handanweisung. Hogrefe, Göttingen
40. Deurenberg P, van der Kooy K, Leenen R, Weststrate JA, Seidell JC (1991) Sex and age specific prediction formulas for estimating body composition from bioelectrical impedance: a cross-validation study. Int J Obesity 15:17–25
41. Blum WF, Englaro P, Hanitsch S, et al. (1997) Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J Clin Endocr Metab 82: 2904–2910
42. von Prittwitz S, Blum WF, Ziegler A, Scharmann S, Remschmidt H, Hebebrand J (1997) Restrained eating is associated with low leptin levels in underweight females. Mol Psychiatry 2: 420–422
43. Kinzl JF, Traweger C, Trefalt E, Mangwerth B, Biebl W (1999) Dietitians: are they a risk group for eating disorders? European Eating Disorders Review 7: 62–67
44. Lorger C, Leitzmann C (1979) Ernährungsgewohnheiten von Öcotrophologiestudenten. Ernährungsumschau 26:181–185
45. Johnston CS, Christopher FS (1991) Anorexic like behaviors in dietetic majors and other student populations. J Nutr Educ 23:148–153
46. Fairburn CG, Cooper Z, Doll HA, Norman P, O'Connor M (2000) The natural course of bulimia nervosa and binge eating disorder in young women. Arch Gen Psychiat 57:659–665
47. Hebebrand J, Fichter M, Gerber G, et al. (2002) Genetic Predisposition to Obesity in Bulimia Nervosa: A Mutation Screen of the Melanocortin-4 Receptor Gene. Mol Psychiatry 7:647–651
48. Bulik CM, Sullivan PF, Fear JL, Pickering A (2000) Outcome of anorexia nervosa: eating attitudes, personality, and parental bonding. Int J Eat Disord 28: 139–147
49. Gendall KA, Sullivan PF, Joyce PR, Bulik CM (1997) Food cravings in women with a history of anorexia nervosa. Int J Eat Disord 22(4):403–409
50. Rosenvinge JH, Mouland SO (1990) Outcome and prognosis of anorexia nervosa. A retrospective study of 41 subjects. Br J Psychiatry 156:92–97
51. Exner C, Hebebrand J, Remschmidt H, Wewetzer C, Ziegler A, Herpertz S, Schweiger U, Blum WF, Preibisch G, Heldmaier G, Klingenspor M (2000) Leptin suppresses semi-starvation induced hyperactivity in rats: implications for anorexia nervosa. Molecular Psychiatry 5:476–481