THE EATING DISORDER bulimia nervosa is characterized by recurrent binge eating, compensatory behaviors to avoid weight gain, and related behavioral and physiological symptoms. Studies of eating behavior in bulimia nervosa have demonstrated impaired postigestive satiety (1), possibly associated with diminished responsiveness in satiety-related pathways involving serotonin or other hypothalamic neurotransmitters (2, 3).

Leptin, the protein product of the ob gene, is thought to influence weight regulation by acting in the central nervous system to decrease food intake, as recently reviewed (4–6), although there are limited data on the magnitude of this effect in primates and humans (7, 8). In rodents, leptin administration decreases meal size (9, 10), suggesting that decreased leptin function could contribute to diminished satiety responses and large binge meals in bulimia nervosa. Additionally, alteration in leptin function affects other neuroendocrine systems, as illustrated by the fact that decreased blood thyroid hormone concentrations may be associated with abnormalities in eating patterns and neuroendocrine regulation in bulimia nervosa (11). Possibly, alterations in eating patterns, metabolic rate, and neuroendocrine regulation in bulimia nervosa could contribute to abnormalities in eating patterns, metabolic rate, and neuroendocrine regulation in bulimia nervosa.

To test the hypothesis that abnormal regulation of leptin may be associated with abnormalities in eating patterns and neuroendocrine hormone levels in bulimia nervosa, this study compared serum leptin concentrations in carefully characterized out-patients meeting diagnostic criteria for bulimia nervosa to results for weight-matched healthy control subjects. Studies were also conducted in individuals who had recovered from bulimia nervosa to assess whether postulated abnormalities in leptin regulation persist after symptom remission.

Subjects and Methods

Subjects

Subjects were recruited from university-affiliated eating disorder programs and from the community for psychobiological studies including serotonin-related neuroendocrine and behavioral assessments (11, 12). Diagnostic evaluations were based on a modified version of the Schedule for Affective Disorders and Schizophrenia-Life Version (13). The patient group included women who met DSM-III-R criteria for bulimia nervosa (14), with the additional criteria of binge eating and purging, on the average, at least three times per week over the preceding 6 months. The remitted group included women who had previously met these modified criteria but had been abstinent from binge eating and purging and had experienced normal menstrual cycles for 3 or more months before study.

The patient and remitted groups had been free of major depression, alcoholism, and substance abuse disorders for at least 6 months and free of psychotropic medications for at least 8 weeks before study. The control group included women with no history of an eating disorder or other major psychiatric disorder. Subjects were at normal weight [body mass index (BMI), 18–26 kg/m²], had not been pregnant or used oral contraceptives within the preceding 6 months, and were in good medical health as assessed by medical history, physical examination, and baseline laboratory studies, including pregnancy and toxicology screening tests. Subjects abstained from alcoholic beverages for at least 1 week before study. The study protocol was approved by the institution’s human studies review board, and all subjects gave written informed consent before study participation.
Procedures

Subjects were admitted to the Clinical Research Center for two neuroendocrine study days, scheduled during the follicular phase of the menstrual cycle (with the exception of one amenorrheic bulimic subject). After an overnight fast and bed rest on the in-patient unit, on the first in-patient day two baseline blood samples for leptin determination were obtained through an iv catheter at approximately (884) and (935) h. Additional baseline hormone measurements included serum PRL and cortisol as well as estradiol, progesterone, T3, free T4, and TSH obtained on the second study day 24 h later (72 h later for two subjects). Percent body fat was calculated based on skinfold measurements (15, 16).

Laboratory methods

Serum samples were stored at −70 C until analyzed by immunoassay, as previously described (12, 17).

Data analysis

Group data are presented as the mean ± sd (mean ± sem in Fig. 1). Initial review of hormone data revealed that 1 participant in each subject group had a baseline estradiol level more than 3 sd greater than the group mean. To avoid potentially confounding outlier effects of elevated estradiol on other neuroendocrine measures, results for these 3 individuals were excluded from subsequent data analysis. Descriptive characteristics for the remaining 18 patients with bulimia nervosa, 15 remitted individuals, and 20 healthy controls were compared by ANOVA or by Kruskal-Wallis test for variables not normally distributed. The two baseline leptin determinations for each subject were averaged to help minimize sampling effects associated with pulsatile variations (18). Serum leptin concentrations were compared across study groups by analysis of covariance, adjusting for percent body fat. Statistical significance (two-sided) for separate preplanned comparisons of the bulimic and remitted groups was determined by partial correlation, adjusting for percent body fat, with leptin and other baseline hormone values was assessed within each subject group by partial correlation, adjusting for percent body fat, with the significance level set at P < 0.01 to adjust for multiple tests.

Results

The subject groups were not significantly different in age or weight-related measures (Table 1). For the bulimia nervosa group, the frequency of binge eating episodes was 6.0 ± 2.7/week, and the frequency of self-induced vomiting was 6.2 ± 3.3 episodes/week. For the remitted group, the duration of remission was 43 ± 29 months. Serum leptin was significantly correlated with percent body fat in the bulimic group (r = 0.707; P = 0.001), in the remitted group (r = 0.722; P = 0.002), and in the controls (r = 0.615; P = 0.004).

Comparison of serum leptin concentrations across subject groups by analysis of covariance yielded a significant main effect for diagnostic group (F = 4.40; P = 0.018), as well as for the percent body fat covariate term (F = 37.1; P < 0.0001). The serum leptin concentration in the bulimic and remitted groups was significantly lower than that in controls (Fig. 1).

In the bulimic patient group, there was a trend toward a correlation between serum leptin concentration and frequency of binge eating (r = −0.40; P = 0.098); leptin was not significantly correlated with the frequency of self-induced vomiting (r = −0.17). For the remitted group, the serum leptin concentration was not significantly correlated with the duration of remission.

The serum leptin concentration was not significantly correlated with other baseline hormone levels or with age within any of the subject groups. As described previously, serum PRL levels were low in the bulimia nervosa group (P = 0.004), and free T4 levels were low in both the bulimic (P = 0.0004) and remitted (P = 0.002) patient groups compared with the control values (12). Reanalysis of leptin values including the three individuals with elevated estradiol levels demonstrated group differences similar to the findings reported above.

Discussion

This study found that nonhospitalized, normal weight women with bulimia nervosa had significantly decreased serum leptin levels compared with age- and weight-matched healthy controls. The trend toward an inverse correlation between serum leptin levels and frequency of binge episodes is consistent with the hypothesis that impaired hypothalamic leptin function contributes to abnormal eating patterns, possibly involving blunted satiety responses. This effect could involve an interaction with serotonergic satiety pathways (19). Based on preclinical findings (4), decreased leptin function may contribute to low thyroid hormone levels in bulimia nervosa (12, 20–22) as well as to abnormalities in hypothalamic-pituitary-gonadal axis regulation (23–25). These relationships could be further clarified through studies of physiological responses to leptin administration in this patient group.

The results of this study are consistent with other recent reports indicating that plasma leptin concentrations in patients with current symptoms of bulimia nervosa were significantly lower than those in healthy controls (26, 27). In contrast to these results, a previous investigation found that the serum leptin concentration was not significantly different in women with bulimia nervosa and healthy controls.

![Fig. 1. Comparison of baseline serum leptin concentrations across study groups (mean ± sem), adjusted for percent body fat. Serum leptin was significantly lower in patients with bulimia nervosa (BN; n = 18) than in controls (n = 20; *, P = 0.02). Similarly, serum leptin levels in individuals recovered from bulimia nervosa (BN-R; n = 15) were significantly lower than the control values (**, P = 0.01).](https://academic.oup.com/jcem/article-lookup/doi/65/12/18245/1162389)
matched for BMI (28). In the latter report, however, it is unclear whether subjects were studied after an overnight fast, whether subject groups were matched for percent body fat, and whether patients were studied during a phase of stable body weight. In another report, serum leptin levels obtained after an overnight fast in patients with bulimia were similar to control values, although the extent to which these groups were matched for BMI or percent body fat was not indicated (29).

A potential limitation regarding the study findings in both the symptomatic and recovered eating disorder patients relates to the fact that the serum leptin concentration is sensitive to short-term changes in food intake and to changes in body weight (30–32). Thus, in a mixed sample of patients with anorexia nervosa and bulimia nervosa, the plasma leptin concentration was significantly correlated with estimated caloric intake over the 48-h before study as well as with body fat mass (33), although plasma leptin levels were not immediately affected by binge eating/purging episodes in a bulimic case report (34). In anorexia nervosa, leptin values are correlated with BMI, with preliminary evidence for an elevated ratio of cerebrospinal fluid to serum leptin concentrations (17, 35–37).

An additional finding in this study was that serum leptin levels in women who had recovered from bulimia nervosa were significantly lower than control values. Thus, decreased leptin in symptomatic bulimic patients may reflect a stable biological trait. Given that patients recovered from bulimia nervosa appear to have abnormalities in leptin regulation, future laboratory studies to assess whether there are persistent abnormalities in meal patterns and satiety responses in this subject group would be of interest.

In contrast to the results presented here, a recent study did not find a significant difference in leptin levels between admitted bulimic patients and controls (38). In this latter study, however, the recovered individuals were at a significantly higher BMI than the controls, and data were not available on percent body fat, which may be a better predictor than BMI of leptin levels in eating disorder patients (39). Although in the current study the minimum time for abstinence from binge eating and purging was briefer than in the previous report (38), correlational analysis did not show a relationship between serum leptin concentrations and duration of symptom remission.

Although the resting metabolic rate was not measured in this study, the findings are consistent with the possibility that decreased leptin function contributes to abnormally low caloric requirements for maintaining stable weight (40) and abnormally decreased resting metabolic rate in bulimia nervosa (21, 41). If decreased leptin function were to predate the onset of bulimia nervosa, it could contribute to the increased efficiency in energy utilization and unwanted weight gain (42), prompting the recurrent dieting that commonly precedes the onset of the disorder (43, 44).

Further research is needed to identify factors contributing to altered serum leptin levels in bulimia nervosa. A familial tendency toward obesity has been reported in bulimia nervosa (45), although this does not appear to be associated with leptin gene mutations (46). Sustained weight loss has been shown to result in a persistent decrease in serum leptin concentrations (47, 48). Thus, one contributing factor to low leptin levels in bulimia nervosa could be a tendency for patients to maintain their weight below a physiologically natural (or set-point) weight. A limitation of the current study is the absence of detailed information on weight stability and nutritional intake (including caloric loss through self-induced vomiting for the bulimia nervosa patient group) during the days preceding the subjects’ admission to the clinical research center. Further studies including these data as well as measurements of metabolic rate would be helpful in clarifying whether a net reduction in caloric intake contributes to the decreased serum leptin levels observed in the patient groups.

In summary, this study found that patients with bulimia nervosa as well as individuals who had recovered from bulimia nervosa had significantly lower serum leptin levels than healthy controls matched for BMI and percent body fat. The results are consistent with the hypothesis that decreased leptin function contributes to impaired postgestive satiety, neuroendocrine abnormalities, and abnormally low resting metabolic rate in bulimia nervosa.

Acknowledgments

We gratefully acknowledge the assistance of the nursing and research staffs of the General Clinical Research Center at Beth Israel Deaconess Medical Center.

References


