ORIGINAL RESEARCH

Psychiatric symptoms and leptin in obese patients who were bariatric surgery candidates

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Objective: There is a significant relationship between obesity and common mental symptoms (depression and anxiety symptoms). But the association between depression (or anxiety symptoms) and serum leptin is still unclear and controversial, despite the growing body of evidence supporting the existence of "leptin resistance" in obese persons. So we investigated whether common mental symptoms, obesity, and the interactive effect of these two factors have a relationship with leptin in obese patients who were candidates for bariatric surgery.

Methods: In all, 139 participants (mean age: 31.4 years, standard deviation: 9.3 years, 73.4% female) were enrolled at an obesity treatment center in southern Taiwan. Serum leptin levels and body mass index (BMI) were measured. The Chinese Health Questionnaire and Taiwanese Depression Questionnaire were administered.

Results: The mean BMI of our participants was 39.4 kg/m^2 ($\pm$6.8), and the mean leptin level was 24.5 ng/mL ($\pm$9.4). In the multivariate regression models, Chinese Health Questionnaire-by-BMI and Taiwanese Depression Questionnaire-by-BMI interaction terms remained significant predictors of leptin level (β=0.16, $P<0.0001$; β=0.04, $P<0.0001$, respectively), after adjustment for age, sex, and history of hypertension, diabetes, and hyperlipidemia, despite the inverse correlation between Chinese Health Questionnaire (or Taiwanese Depression Questionnaire) and leptin. In addition, female patients had significantly higher leptin levels than male patients.

Conclusion: The present findings confirmed that the relationship between common mental symptoms and leptin is modulated by obesity in severely obese patients. Future studies should focus on further measures of leptin receptors or signaling on the basis of these interactive effects in psychiatry.

Keywords: leptin, depression, anxiety, common mental disorder, obesity

Background

Depressive disorder is a prevalent mental disorder worldwide and is also a huge burden on public health globally.[1] It is a complex and heterogeneous disorder and has diverse symptomatologies and psychopathologies. Common mental disorder is a diagnostic entity for nonpsychotic, depressive, and anxiety disorders. It leads to substantial morbidity worldwide, and its prevalence is increasing.[2] Body mass index (BMI) is a simple index of weight-for-height (kilograms per meter squared) that is commonly used to classify underweight, overweight, and obesity. Obesity is defined by the WHO as BMI >30 kg/m^2. Obesity leads to several chronic diseases such as hypertension, diabetes, hyperlipidemia, cardiovascular events, and stroke. Several epidemiological and clinical studies have suggested a link between obesity and psychiatric comorbidity.[3] Obesity is positively associated with several mental disorders, especially mood and anxiety disorders.[4] Adipose tissue secretes large amounts of proinflammatory cytokines. Hypercytokinemia, from a chronic inflammatory state of obesity, is frequently

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associated with depressive symptoms.[5] At the same time, leptin may have its own role in the association between obesity and common mental disorders.

Leptin is an adipocyte hormone and is transported across the blood–brain barrier to exert its central effects. Leptin regulates human energy homeostasis. Its secretion is proportionate to the fat stores of the body; starvation or food deprivation reduces leptin levels.[6] Other regulators of circulating leptin levels include sex, age, and food intake. In addition to the most common role of leptin in metabolism, its receptors are widely distributed in brain areas related to emotional responses, such as the hippocampus. However, the neurobiological mechanisms of leptin and their role in the regulation of moods are still unknown.[7] In an animal study, leptin was dysregulated in chronic unpredictable stress models and chronic social defeat models, which were suggested to meet the criteria for the validity of animal models of symptoms of depression. Leptin treatment overcame behavioral deficits in the forced swim test.[8] It could be speculated that leptin has a potential antidepressant efficacy. However, in obese humans, chronic overeating results in a tendency to develop leptin resistance, despite the high leptin levels observed. Clinical data on the association between leptin and depression are limited and controversial, even in obese patients.

It has been hypothesized that leptin resistance blunts its central action, despite the high levels of leptin in obese persons. In other words, it is not the absolute serum leptin concentration but its dysfunction in the central nervous system that may contribute to a causal relationship with depression.[7] However, the high leptin levels in obese persons are still considered an indication of leptin resistance in clinical observation. Two previous studies reported an association between leptin and depressive symptoms that was modulated by abdominal adiposity in older community-dwelling persons.[9,10] A key question to be addressed is whether the leptin hypothesis can serve as a common biological factor for comorbidity of obesity and common psychiatric symptoms. Therefore, we aimed to explore the association among leptin levels, adiposity, psychiatric symptoms, and their interaction in bariatric surgery candidates.

Methods
Subjects
Most of our subjects were patients with morbid obesity. Forty-six of the patients who were overweight or obese (BMI <35 kg/m²) had obesity-related health problems, such as diabetes, hypertension, gastroesophageal reflux disease, or

metabolic syndrome. Our multidisciplinary team (including dietitians, endocrinologists, gastroenterologists, psychiatrists, and surgeons) surveyed and evaluated these patients who were unable to reduce body weight through diet control, behavioral modification, or pharmacological therapy, and determined they would be candidates for bariatric surgery at E-Da Hospital, Kaohsiung, Taiwan. From November 2006 to February 2009, a total of 139 severely obese bariatric surgery candidates were enrolled in our cross-sectional study. Patients with psychotic or eating disorders were excluded. All participants provided written informed consent. The study design was approved by the institutional review board of E-Da Hospital (Kaohsiung, Taiwan).

Serum leptin level
The leptin level is not stable throughout the day and has no clear diurnal pattern.[6] In order to avoid the effect of food intake, fasting venous blood was withdrawn in the morning with no consumption of food overnight. Venous blood sampling was performed first, and then the serum was frozen at −80°C for later measurement of leptin. The serum leptin concentration was measured using a commercially available radioimmunoassay kit.

Screening tools for common psychiatric symptoms
Chinese Health Questionnaire
The Chinese Health Questionnaire (CHQ) is a 12-question, 2-reverse questions, 0–1-point questionnaire used to screen somatic and psychic anxiety symptoms, social dysfunction, self-confidence, and hope, all suggesting the nonpsychotic, depressive, and anxiety symptoms of common mental disorders. The questionnaire was derived from the General Health Questionnaire, with the addition of specially designed, culturally relevant items.[11] For minor psychiatric morbidities, the questionnaire had sensitivity and specificity of 70% and 95%, respectively, in a community study.[12] Cronbach's α of 0.84 and internal consistency of 0.79 were demonstrated for the CHQ.[13] The cutoff point in Taiwan community surveys is ≥5 points.

Taiwanese Depression Questionnaire
The Taiwanese Depression Questionnaire (TDQ) is an 18-question, 0–3-point questionnaire used for screening clinically depressive symptoms. The questionnaire is a culturally specific depression self-rating instrument for use in Taiwan.[14] The TDQ has a Cronbach's α of 0.90 and sensitivity and specificity of 0.89 and 0.92, respectively. The cutoff point in the Taiwan community population is ≥19 points.

Statistical analysis

Descriptive results regarding continuous variables were presented as the mean (standard deviation [SD]), and categorical variables were given as count and percentages. We also categorized the TDQ score by severity (no to minimal, mild, moderate to severe) to conduct an analysis to compare the leptin levels among each subgroup. All factors (age, sex, BMI, history of hypertension, diabetes, hyperlipidemia, CHQ score, and TDQ score) were included in five multiple linear regression models to identify abilities to independently predict leptin levels. In model 1, we included sex, age, BMI, history of hypertension, diabetes, and hyperlipidemia as independent variables. The CHQ score was added to the above six variables in model 2, and the TDQ score was added to the same six variables in model 4. In addition, we tested the interactive effect between the CHQ (or TDQ) score and BMI by standardizing the two and multiplying them with each other, and then used them as a new variable. So, in linear model 3 and model 5, the terms CHQ × BMI and TDQ × BMI were introduced, respectively, in addition to the preserved independent variables (sex, age, history of hypertension, diabetes, and hyperlipidemia, CHQ or TDQ score). All analyses were performed with SPSS 19.0 version for Windows (StataCorp LP, College Station, TX, USA). The study was approved by the Institutional Review Board of E-Da Hospital.

Results

Demographic and clinical characteristics

With regard to demographic and clinical characteristics, the female-to-male ratio of the obese patients was approximately 3:1, the average age was 31.4 years (±9.3), and BMI ranged from 26.3 kg/m^2 to 67.5 kg/m^2, with a mean value of 39.4 kg/m^2 (±6.8). The mean CHQ and TDQ scores were 4.1 and 14.7, respectively. The leptin level ranged from 8 ng/mL to 56 ng/mL with a mean level of 24.5 ng/mL (±9.4). Approximately 25% of patients recruited had a medical history of hypertension

and 10% had diabetes mellitus and hyperlipidemia. Women had more common mental symptoms and higher plasma leptin levels. Men had greater BMI and more history of hypertension (Table 1). There was no significant difference in leptin levels among the three subgroups by severity of depression (Figure 1).

Multivariate linear regression models

In model 1, female sex (β coefficient =8.36, $P<0.0001$) and BMI (β coefficient =0.76, $P<0.0001$) were significantly associated with leptin level. In model 2, female sex and BMI were statistically significant (β coefficient =8.19, $P<0.0001$; β coefficient =0.76, $P<0.0001$, respectively) but not the CHQ score. In model 3, the CHQ-by-BMI interaction term (CHQ × BMI) was significantly associated with leptin (β coefficient =0.16, $P<0.0001$), indicating that CHQ-by-BMI interaction was detected. However, the CHQ score itself was inversely correlated to leptin (β coefficient =−6.20, $P<0.0001$; Table 2). The R^2 value was 0.419. Based on the these findings, a positive interactive effect between CHQ score and BMI on leptin level was confirmed. In model 4, female sex and BMI were still significant predictors of leptin level (β coefficient =8.27, $P<0.0001$; β coefficient =0.76, $P<0.0001$, respectively). In model 5, the TDQ-by-BMI interaction term (TDQ × BMI) and female sex were significant predictors of leptin level (β coefficient =0.04, $P<0.0001$; β coefficient =7.44, $P<0.0001$, respectively), whereas the TDQ score was negatively correlated (β coefficient =−1.40, $P<0.0001$). The R^2 value was 0.397 (Table 3). This model also confirmed that BMI significantly moderates the relationship between the TDQ score and the leptin level.

Discussion

In this study, our main findings included that obesity and the depression (or anxiety symptoms)-by-obesity interaction were both significantly associated with the leptin level, after

Table 1 Demographics and clinical characteristics of the obese patients

	All subjects (N=139)	Men (n=37)	Women (n=102)	*P*-value
Age, years, mean (SD)	31.4 (9.3)	29.5 (9.3)	32.0 (9.3)	0.168
BMI, kg/m^2, mean (SD)	39.4 (6.8)	41.5 (6.3)	38.7 (6.9)	0.036
History of hypertension, n (%)	35 (25.2)	16 (43.2)	19 (18.8)	0.003
History of diabetes, n (%)	15 (10.8)	6 (16.2)	9 (8.9)	0.222
History of hyperlipidemia, n (%)	15 (10.8)	6 (16.2)	9 (8.9)	0.222
CHQ score, mean (SD)	4.1 (2.5)	3.4 (2.4)	4.4 (2.5)	0.029
TDQ score, mean (SD)	14.7 (10.8)	11.9 (9.9)	15.8 (11.0)	0.064
Leptin, ng/mL, mean (SD)	24.5 (9.4)	19.4 (7.6)	26.4 (9.4)	<0.0001

Abbreviations: BMI, body mass index; CHQ, Chinese Health Questionnaire; TDQ, Taiwanese Depression Questionnaire.
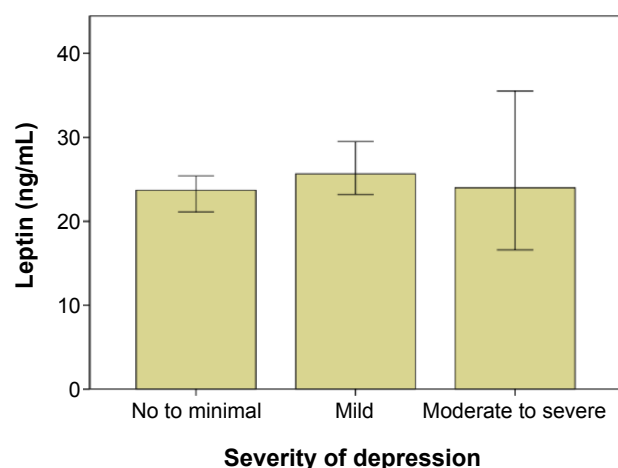
Figure 1 Median levels of leptin by severity of depression.
Notes: TDQ scores: 0–18, no to minimal depression; 19–28, mild depression; ≥29, moderate to severe depression.
Abbreviation: TDQ, Taiwanese Depression Questionnaire.

adjustment for age, sex, and history of hypertension, diabetes, and hyperlipidemia, despite the inverse correlation between CHQ (or TDQ) and leptin. There are few studies that have focused on the prevalence of psychiatric disorders in Asian patients who seek obesity treatment. Lin et al explored the high prevalence of psychiatric disorders, especially mood disorders and anxiety disorders, in this population.[15] The present study, to our knowledge, is the first to investigate the possible simultaneous influence and relationship among obesity, common psychiatric symptoms (depression and anxiety symptoms), and serum leptin level in ethnic Chinese morbidly obese patients. Some previous studies confirmed the significant association between leptin and depressive symptoms in an overlapping population (patients with metabolic syndrome and with type 2 diabetes),[16,17] but the present study further focused on severely obese patients who were candidates for bariatric surgery. Milaneschi et al reported that the association between leptin and depressive symptoms was modulated by abdominal adiposity.[10] But they used leptin-by-obesity as a predictive variable and

depressive symptoms as a dependent variable instead. Leptin level, rather than depression, was used as a dependent variable in our study due to the presence of more confounders in predicting depression, such as other endocrine systems (estrogen, hypothalamus–pituitary–adrenal axis), and psychosocial factors that need to be controlled. Morris et al reported depression was a significant predictor of leptin levels, but further adjustment for BMI eliminated the association between them.[18] This means the association between depression and leptin varies based on obesity status. Their study also used leptin levels as dependent variables and showed that overall severity of depression (by the Beck Depression Inventory II) was positively correlated with leptin levels.

The sex-specificity bias toward females, compared with males, showed higher levels of leptin in our study, consistent with the established literature.[17,19,20] Even the finding that healthy women have higher leptin levels than men has been confirmed consistently.[21] The reason for the sex difference needs to be elucidated. However, obese women usually have more self-distress from the stigma of obesity (especially in Asia, where the criteria for overweight/obesity is stricter and lower than in the Western world), more dissatisfaction with their body image, and more mood disorders and eating problems.[15] So they should be afforded more attention and intervention in obesity treatment.

A few studies found that leptin levels were higher in patients with depression,[22–24] with a bias toward females, even in premenopausal women.[25] However, other studies reported that low leptin levels were associated with depression.[26–28] Moreover, decreased leptin levels were observed in female patients with postpartum depression[29] and in reproductive-age female populations.[30] A lower cerebrospinal fluid leptin level was also found in suicide attempters with depression.[31] In our study, the TDQ score was inversely associated with the leptin level, which meant that the negative relationship between severity of depressive symptoms and leptin was

Table 2 Multiple linear regression models predicting leptin level by common mental symptoms

	Model 1*		Model 2**		Model 3***	
	β coefficient (95% CI)	*P*-value	*β* coefficient (95% CI)	*P*-value	*β* coefficient (95% CI)	*P*-value
Female	8.36 (5.49 to 11.23)	<0.0001	8.19 (5.28 to 11.09)	<0.0001	7.29 (4.27 to 10.31)	<0.0001
Age	−0.08 (−0.22 to 0.07)	0.288	−0.08 (−0.23 to 0.64)	0.270	−0.11 (−0.26 to 0.04)	0.149
BMI	0.76 (0.57 to 0.94)	<0.0001	0.76 (0.58 to 0.95)	<0.0001	NA	
Hypertension	−1.49 (−4.85 to 1.87)	0.382	−1.51 (−4.88 to 1.86)	0.377	−3.02 (−6.55 to 0.51)	0.093
Diabetes	−0.67 (−5.21 to 3.88)	0.772	−0.60 (−5.16 to 3.95)	0.794	−0.34 (−5.11 to 4.44)	0.890
Hyperlipidemia	−3.55 (−7.66 to 0.57)	0.090	−3.63 (−7.75 to 0.50)	0.084	−2.62 (−6.91 to 1.68)	0.230
CHQ score	NA		0.20 (−0.30 to 0.70)	0.425	−6.20 (−8.03 to −4.37)	<0.0001
CHQ × BMI	NA		NA		0.16 (0.12 to 0.21)	<0.0001

Notes: *Model 1 R^2 is 0.466; **Model 2 R^2 is 0.469; ***Model 3 R^2 is 0.419.
Abbreviations: BMI, body mass index; CHQ, Chinese Health Questionnaire; CI, confidence interval; NA, not applicable.

Table 3 Multiple linear regression models predicting leptin level by depressive symptoms

	Model 1*		Model 4**		Model 5***	
	β coefficient (95% CI)	*P*-value	β coefficient (95% CI)	*P*-value	β coefficient (95% CI)	*P*-value
Female	8.36 (5.49 to 11.23)	<0.0001	8.27 (5.35 to 11.19)	<0.0001	7.44 (4.36 to 10.53)	<0.0001
Age	−0.08 (−0.22 to 0.07)	0.288	−0.08 (−0.22 to 0.07)	0.299	−0.15 (−0.30 to 0.01)	0.061
BMI	0.76 (0.57 to 0.94)	<0.0001	0.76 (0.57 to 0.94)	<0.0001	NA	
Hypertension	−1.49 (−4.85 to 1.87)	0.382	−1.49 (−4.86 to 1.88)	0.384	−2.75 (−6.34 to 0.83)	0.131
Diabetes	−0.67 (−5.21 to 3.88)	0.772	−0.73 (−5.29 to 3.84)	0.754	−0.68 (−4.95 to 4.81)	0.978
Hyperlipidemia	−3.55 (−7.66 to 0.57)	0.090	−3.61 (−7.75 to 0.53)	0.087	−2.14 (−6.52 to 2.24)	0.335
TDQ score	NA		0.02 (−0.09 to 0.13)	0.709	−1.40 (−1.85 to −0.95)	<0.0001
TDQ × BMI	NA		NA		0.04 (0.03 to 0.05)	<0.0001

Notes: *Model 1 R^2 is 0.466; **Model 4 R^2 is 0.467; ***Model 5 R^2 is 0.397.
Abbreviations: BMI, body mass index; CI, confidence interval; TDQ, Taiwanese Depression Questionnaire; NA, not applicable.

compatible with the role of leptin insufficiency in depression (or leptin might be a novel antidepressant). But in these subjects with greater BMI, depression was associated with leptin levels after adding an interactive effect. That is to say, the result of an interactive effect between depression and obesity in predicting leptin levels was consistent with the hypothesis of leptin resistance in depression. Leptin is ineffective in inhibiting food intake and increasing energy expenditure in obese persons but leads to a reduction in adipose tissue and weight loss in persons with normal weight.[32] This suggests that leptin resistance in obese persons also blunts this hormone's potential antidepressant efficacy. So we could expect that these obese patients with depression would have a better chance to respond to the leptin treatment after the obesity treatment. The underlying nature of leptin insufficiency versus leptin resistance in depression deserves further clinical research.

Data on the association between leptin and anxiety symptoms are relatively lacking. We reported a negative correlation between common mental symptoms (including anxiety symptoms) and leptin in our study. But another interactive effect between common mental symptoms and obesity also significantly predicted leptin levels. Two recent studies reported partially similar findings. Yoshida-Komiya et al reported that 29 reproductive-age women with mild depressive and anxious states (including five overweight subjects) had lower levels of leptin than healthy volunteers.[30] Our study enrolled a higher total number of participants and number of obese participants than the aforementioned study. Lawson et al recruited 64 women and reported an inverse relationship between leptin and anxiety symptoms, but most Hamilton Rating Scale for Anxiety scores in the study were within the normal range.[28] Our study used the CHQ as a localized and validated screening tool to present the distribution of scores.

There are some limitations in our study. First, this was a cross-sectional investigation and therefore, causality cannot

be determined. Second, depressive and anxiety symptoms were obtained from self-reported questionnaires, with a lack of further clinical evaluation and diagnosis by mental health professionals. There perhaps was a possibility that the obese patients would conceal their true underlying psychopathologies and try not to let mental problems affect their optimal obesity treatment. Third, our study did not include the effect of the hypothalamus–pituitary–adrenal axis on obesity and depression or the mutual interaction between leptin and cortisol.[33,34] Finally, as we mentioned earlier, leptin resistance may play an important role in the leptin hypothesis, and the interactive effect of leptin level and BMI may further indicate the severity of leptin resistance. We still need more structured and longitudinal study designs and analyses to clarify this interaction in association with psychiatric symptoms.

Conclusion

In conclusion, some of our findings have duplicated those of previous studies and have shown the importance of interactive effects among depression, anxiety, and obesity relative to leptin in psychoendocrinology, even in obese patients. Future studies should focus on further measures of leptin receptors or signaling on the basis of these interactive effects in psychiatry.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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