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

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$^2$ (±6.8), and the mean leptin level was 24.5 ng/mL (±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 ($\beta=0.16, P<0.0001$; $\beta=0.04, P<0.0001$, 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
associated with depressive symptoms. 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. 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. 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. 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. 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. 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. 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. For minor psychiatric morbidities, the questionnaire had sensitivity and specificity of 70% and 95%, respectively, in a community study. Cronbach’s α of 0.84 and internal consistency of 0.79 were demonstrated for the CHQ. 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. 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/m² to 67.5 kg/m², with a mean value of 39.4 kg/m² (±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 R² value was 0.419. Based on 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 R² 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

<table>
<thead>
<tr>
<th></th>
<th>All subjects (N=139)</th>
<th>Men (n=37)</th>
<th>Women (n=102)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>31.4 (9.3)</td>
<td>29.5 (9.3)</td>
<td>32.0 (9.3)</td>
<td>0.168</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>39.4 (6.8)</td>
<td>41.5 (6.3)</td>
<td>38.7 (6.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>35 (25.2)</td>
<td>16 (43.2)</td>
<td>19 (18.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>15 (10.8)</td>
<td>6 (16.2)</td>
<td>9 (8.9)</td>
<td>0.222</td>
</tr>
<tr>
<td>History of hyperlipidemia, n (%)</td>
<td>15 (10.8)</td>
<td>6 (16.2)</td>
<td>9 (8.9)</td>
<td>0.222</td>
</tr>
<tr>
<td>CHQ score, mean (SD)</td>
<td>4.1 (2.5)</td>
<td>3.4 (2.4)</td>
<td>4.4 (2.5)</td>
<td>0.029</td>
</tr>
<tr>
<td>TDQ score, mean (SD)</td>
<td>14.7 (10.8)</td>
<td>11.9 (9.9)</td>
<td>15.8 (11.0)</td>
<td>0.064</td>
</tr>
<tr>
<td>Leptin, ng/mL, mean (SD)</td>
<td>24.5 (9.4)</td>
<td>19.4 (7.6)</td>
<td>26.4 (9.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CHQ, Chinese Health Questionnaire; TDQ, Taiwanese Depression Questionnaire.
Table 2 Multiple linear regression models predicting leptin level by common mental symptoms

<table>
<thead>
<tr>
<th>Model 1*</th>
<th>Model 2**</th>
<th>Model 3***</th>
</tr>
</thead>
<tbody>
<tr>
<td>β coefficient (95% CI)</td>
<td>P-value</td>
<td>β coefficient (95% CI)</td>
</tr>
<tr>
<td>Female</td>
<td>8.36 (5.49 to 11.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.08 (-0.22 to 0.07)</td>
<td>0.288</td>
</tr>
<tr>
<td>BMI</td>
<td>0.76 (0.57 to 0.94)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-1.49 (-4.85 to 1.87)</td>
<td>0.382</td>
</tr>
<tr>
<td>Diabetes</td>
<td>-0.67 (-5.21 to 3.88)</td>
<td>0.772</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>-3.55 (-7.66 to 0.57)</td>
<td>0.090</td>
</tr>
<tr>
<td>CHQ score</td>
<td>NA</td>
<td>0.20 (-0.30 to 0.70)</td>
</tr>
<tr>
<td>CHQ x BMI</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes: *Model 1 R² is 0.466; **Model 2 R² is 0.469; ***Model 3 R² is 0.419.

Abbreviations: BMI, body mass index; CHQ, Chinese Health Questionnaire; CI, confidence interval; NA, not applicable.
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

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## Disclosure

The authors report no conflicts of interest in this work.

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

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ coefficient (95% CI)</td>
<td>P-value</td>
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</tr>
<tr>
<td>Hyperlipidemia</td>
<td>−3.55 (−7.66 to 0.57)</td>
<td>0.090</td>
<td>−3.61 (−7.75 to 0.53)</td>
</tr>
<tr>
<td>TDQ score</td>
<td>NA</td>
<td></td>
<td>0.02 (−0.09 to 0.13)</td>
</tr>
<tr>
<td>TDQ × BMI</td>
<td>NA</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
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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.
References