

The role of leptin mediating the relationship between 'Somatic Anxiety' symptoms and major depressive disorder

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Abstract

Background Leptin is a multifunctional hormone with influences on neural circuitry in emotional processing, and it may play a role in the pathophysiology of major depressive disorder (MDD). In this study, we aimed to investigate whether leptin levels were differentiated in patients with MDD and those at genetic high risk of MDD (GHR-MDD) and the relationship between leptin and clinical symptoms.

Methods: Participants (18 drug-naïve MDD, 15 GHR-MDD and 40 healthy controls) completed clinical assessments and provided blood samples for measurement of leptin levels. Leptin levels were compared across all groups and associations between leptin and clinical symptoms were explored and mediation models tested.

Results: We found that leptin was increased in MDD. We also found a correlation between leptin and 'Somatic Anxiety' symptoms in MDD and that leptin was a significant and independent mediator of clinical state and 'Somatic Anxiety' symptoms.

Conclusions: MDD patients occurred with dysregulation of leptin. Additionally, there was a correlation between leptin and 'Somatic Anxiety' symptoms in MDD. The finding of leptin as a significant and independent mediator of clinical state and 'Somatic Anxiety' symptoms suggested leptin plays an indirect effect in somatic depressive symptoms in MDD.

Background

Major depressive disorder (MDD) is one of the most prevalent and disabling disorders worldwide [1]. It is predicted that the second highest worldwide disease burden after heart disease by 2020 will be from MDD [2]. MDD is regarded as a heritable disorder. Genetic epidemiological research has indicated that compared with the general population, people with one first-degree relative with a mood disorder are about 2.8 times more likely to suffer from depressive disorder [3]. However, despite the increased genetic risk, most people at genetic high risk of MDD (GHR-MDD) do not develop MDD. Novel methods of comparing diseased populations and healthy controls could potentially indicate candidate markers of vulnerability and progression to MDD, as well as potential markers for resilience to the disorder.

There is a bidirectional relationship between depressive disorder and obesity: the presence of one disorder increases the risk of developing the other [4]. Furthermore, patients with obesity and their first-degree relatives frequently experience depression, anxiety, and other psychiatric disturbances [5, 6]. Leptin was discovered by Zhang et al [7], as a 16-kD hormone secreted by adipose tissue, that plays a core role in regulating energy intake and expenditure. Leptin can permeate the blood brain barrier (BBB), and play a role in synaptic activity, neuronal morphology, and neuronal development in the central nervous system [8, 9]. The leptin distributed in the brain is related to emotional and cognitive processes, such as the hypothalamus and hippocampus, which has sparked increasing interest in mood disorder [9–11]. Animal models suggest that impaired leptin production may contribute to depression [10, 12]. However, preliminary research in humans has provided conflicting clinical results with both high and low levels of

leptin found in depressed patients [13–15]. Additionally, no consensus on the relationship between leptin levels and the severity of depression symptoms has been reached. These mixed results are likely due to the influence of antidepressants. Therefore, we determined to include only untreated patient with MDD.

Taken together, preliminary research findings indicate that dysregulation of peripheral metabolic markers play an important role in the pathophysiology of MDD, conferring factors influencing vulnerability to MDD to the children who have parents that suffer from MDD.

In this study, we examined the plasma leptin levels of people with untreated MDD, GHR-MDD and in healthy controls (HCs) and evaluated the correlation between leptin and MDD symptoms. In addition, we examined whether blood biomarkers mediated the association between clinical state (MDD, GHR-MDD) and symptoms, based on correlation analyses. We hypothesized that (1) MDD and GHR-MDD occur with dysregulation of leptin; (2) leptin level is significantly correlated with depressive symptoms in MDD; and (3) leptin as a mediator could potentially influence depressive symptoms.

Materials And Methods

Participants

Participants included drug-naïve patients with MDD ($n = 18$), GHR-MDD ($n = 16$) and HCs ($n = 40$), all aged between 13 and 45 years. Drug-naïve MDD patients were recruited from 2014 to 2017 in the Department of Psychiatry at the First Affiliated Hospital of China Medical University and Shenyang Mental Health Center. Participants with GHR-MDD were all first-degree relatives of patients presenting with MDD at the Department of Psychiatry at the First Affiliated Hospital of China Medical University and Shenyang Mental Health Center. HCs were recruited from the local community using advertisements. All participants signed informed consent forms that had been approved by the ethics committee of China Medical University.

Participants with MDD were diagnosed by two trained psychiatrists individually and were included if they met the following criteria: (1) they fulfilled the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL) criteria if younger than 18 years; (2) they fulfilled the Structured Clinical Interview DSM-IV criteria for MDD if 18 years or older; and (3) they had no comorbid diagnosis of psychosis or bipolar disorder, and no history of psychotropic medication. GHR-MDD participants were all first-degree relatives of individuals with MDD who did not meet the criteria for any DSM-IV Axis I disorder. HCs were individuals who did not have a current or previous history of Axis I disorders, and did not have any first-degree relatives with a history of Axis I disorders. Severity of depression and anxiety of all the participants was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D-17) and the Hamilton Anxiety Rating Scale (HAM-A). The multidimensional character ('Somatic Anxiety', 'Psychic Anxiety', 'Core Depressive' and 'Anorexia') of the HAM-D-17 was deemed useful to better understand the psychopathological dimensions of the participants [16].

The study was approved by the Institutional Review Board of the China Medical University and was performed in accordance with the Declaration of Helsinki. Experiments and methods were performed in accordance with approved guidelines and regulations. Demographic and clinical details are presented in Table 1.

Plasma leptin determination

Blood collection was carried out according to standardized protocols, with samples taken between 10:00 AM and 3:00 PM. EDTA was used as an anticoagulant. Plasma samples were centrifuged for 10 min at 2000 rpm and stored at -80°C until analysis. Human Premixed Multi-Analyte Kit (R&D Systems, Inc., Minneapolis, MN, USA) with the Human Magnetic Luminex Assay was used to measure plasma leptin levels. Samples were magnetically labeled using a human magnetic premixed microparticle cocktail of antibodies (Kit Lot Number L120614).

Statistical analyses

We separated the participants into three groups (HC, GHR-MDD and MDD). Either one-way analysis of variances (ANOVAs) or chi-square tests were used to examine the demographic characteristics (age, gender and body mass index [BMI]) and clinical characteristics (duration of illness, first episode, and HAMD and HAMA scores) of the participants. Leptin concentrations were analyzed using one-way analysis of covariance (ANCOVA), with age, gender and BMI as covariates. Post-hoc analyses were performed among the HC, GHR-MDD, and MDD groups using a general linear model.

We used Spearman correlation to analyze the correlation between leptin levels and clinical symptoms in the MDD group. Based on previous correlation analyses, we then used multiple regression analyses to examine the effects of leptin on clinical symptom scores after accounting for age, gender and BMI. Based on these results, a mediation analysis was used to explore whether leptin (as mediator variable) potentially influenced the association between clinical state-MDD and GHR-MDD (causal variable) and clinical symptoms (outcome variable). For the mediation analysis, the PROCESS procedure for SPSS Version 3.2 (Written by Andrew F. Hayes, Ph.D., www.afhayes.com) was used, with a 5000 bias-corrected bootstrap sample for significance testing. We summarized mediators using mean, standard deviation (*SD*), and 95% confidence interval (*CI*).

Significance was set at $p < 0.05$ (two-tailed) for all tests. All analyses were performed using SPSS 22.0.

Results

Demographic and clinical characteristics

There were significant differences in age ($p = 0.014$) among the HC, GHR-MDD, and MDD groups but no significant differences in gender and BMI ($p > 0.05$). The effect of diagnosis on HAMD (Somatic Anxiety,

Psychic Anxiety, Core Depressive, Anorexia, Total scores) [16] and HAMA scores were significant among the HC, GHR-MDD, and MDD groups (all p -values < 0.001; Table 1).

Comparison of plasma concentrations

After controlling for age, gender and BMI, significant group effects were observed in leptin level in the three-group analysis ($p = 0.004$). Post-hoc analysis revealed a significantly higher leptin level in MDD, compared with GHR-MDD ($p = 0.003$) and HC ($p = 0.005$) but no significant difference in leptin between GHR-MDD and HC (Fig. 1).

Correlation between leptin level and clinical symptoms in MDD

In the MDD group, correlation analysis identified a significant positive correlation between leptin level and 'Somatic Anxiety' score on the HAMD ($r = 0.550$, $p = 0.024$; Fig. 2) and no significant correlation between leptin and scores for 'Psychic Anxiety', 'Core Depressive', 'Anorexia', as well as 'Total' scores on the HAMD and HAMA (Table 2). Multiple regression analyses showed that leptin predicted 'Somatic Anxiety' ($\beta = 0.520$, $t = 2.355$, $p = 0.033$).

Mediation analysis

Based on the results of the correlation analyses, we found a correlation between leptin and 'Somatic Anxiety' in the MDD group. We found that leptin (Path AB, $\beta = -0.4752$; 95% CI: -1.0395 to -0.0062) significantly mediated group differences in 'Somatic Anxiety' as measured by the HAMD. As shown in Fig. 3, diagnosis was significantly related to leptin level (Path A, $\beta = -1570.4384$, $t = -2.3583$, $p = 0.0251$), and leptin was significantly positively associated with 'Somatic Anxiety' on the HAMD (Path B, $\beta = 0.0003$, $t = 2.9956$, $p = 0.0056$). Total effect (effect of diagnosis on 'Somatic Anxiety') was also significant (Path C, $\beta = -1.6627$, $t = -4.0111$, $p = 0.0004$). After accounting for leptin as a mediator, the direct effect of diagnosis on 'Somatic Anxiety' was significant (Path C', $\beta = -1.1875$, $t = -2.9603$, $p = 0.0061$).

Discussion

To the best of our knowledge, this was the first study to investigate alterations of leptin in MDD and GHR-MDD. We found that leptin was increased in participants with MDD. Subsequently, we found a correlation between leptin and 'Somatic Anxiety' in MDD, with leptin as a significant and independent mediator of clinical state and 'Somatic Anxiety' symptom.

Dysregulation of leptin in MDD

We found that leptin was increased in the MDD group but failed to find the same change in the GHR-MDD group, suggesting that raised leptin may be a potential vulnerable factor related to MDD. Important symptoms of MDD include loss of appetite and weight loss, and leptin is known to regulate food intake and weight. Although leptin is an anti-obesity hormone associated with decreases in individual weight, patients with obesity appear to display high levels of leptin [17]. The results of studies of leptin levels in MDD have been inconsistent, with both reduced [18, 19] and elevated [20–22] leptin levels found. The variability of these results may be due to subtype heterogeneity in MDD. Clinical symptoms in MDD patients may vary, such as appetite and/or weight increasing and/or decreasing, with subsequent alteration in leptin levels. Furthermore, sexual dimorphism may affect leptin levels, with leptin higher in females than males [23, 24]. One meta-analysis indicated that males who expressed lower adiponectin and high leptin levels had a higher likelihood of developing MDD, but the same was not found in females [25]. One viewpoint put forward is that dysfunction of leptin signaling to the central nervous system, rather than the absolute concentration of leptin, affects mood [26].

The relationship between leptin and symptoms in MDD

In this study, we found a positive correlation between leptin and ‘Somatic Anxiety’ but not for other symptoms. Additionally, leptin significantly and independently mediated the association between diagnosis and ‘Somatic Anxiety’. The ‘Somatic Anxiety’ psychopathological dimension of MDD in the HAM-D-17 includes somatic anxiety, hypochondria, sleep disturbance, general somatic symptoms, and gastrointestinal symptoms [16]. Chirinos et al. demonstrated that leptin was positively associated with somatic depressive symptoms [27]. In another study, a sex difference in the correlation between leptin and severity of depression in type 2 diabetes was found, with a positive association in men but not in women [28]. In a mouse study, leptin was found to reduce depressive behaviors [29]. Evidence from preclinical studies has clearly indicated that leptin exerts antidepressant and anxiolytic effects [30]. These conflicting findings may be explained by the complexity of leptin response as a function of obesity, which is often associated with high levels of leptin. Taken together, the finding suggests that leptin plays a potential role in mediating somatic anxiety symptom in MDD.

Limitations

There are limitations to our study. Firstly, we selected medication-naïve MDD patients to minimize the influence of treatment, resulting in a small sample size that may limit the generalizability of our results as well as our ability to detect relationships between blood biomarkers and symptoms. Future studies with larger sample sizes will be important to further understand the pathophysiology of MDD. Second, this was a cross-sectional study; therefore, subsequent developments in participants with GHR-MDD were unknown. A longitudinal study of GHR-MDD with long-term follow-up is required, with comparisons

between individuals who do and do not develop MDD, allowing for the possibility of developing a better mechanism to determine genetic susceptibility or protective factors for the disorder.

Conclusion

In summary, we found that leptin was increased in MDD and leptin as a vulnerable factor can influence MDD status. Additionally, we found a correlation between leptin and 'Somatic Anxiety' in MDD patients, with leptin as a significant and independent mediator of clinical state and 'Somatic Anxiety' symptom, suggesting leptin plays an indirect effect in somatic depressive symptoms in MDD.

List Of Abbreviations

MDD: major depressive disorder; GHR-MDD: genetic high risk of MDD; BBB: blood brain barrier; HC: healthy control; KSADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children; HAMD-17: 17-item Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; ANOVA: one-way analysis of variance; BMI: body mass index; ANCOVA: one-way analysis of covariance; SD: standard deviation; CI: confidence interval.

Declarations

Ethics Statement

This research was approved by the Medical Research Ethics Committee of the China Medical University and in accordance with the Declaration of Helsinki. All participants gave written informed consent, and the adolescent participants' parents or legal guardian provided written informed consent after receiving a detailed description of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets we applied are available from the corresponding author, provided reasonable requests.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

YZ, YW, FW and YT designed the study. RZ, JS, PW, JL, SW and XJ were collected participants. YZ and JD did the analysis plan. YZ rafted the manuscript. All authors read, contributed to and approved the final manuscript.

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Tables

Table 1 Demographic and clinical characteristics of HC, HR-MDD and drug-naïve MDD.

	HC	GHR-MDD	MDD	F/χ^2 Value	p Value
n	40	15	18		
Age	25.22 (4.84)	30.00(7.46)	23.89(7.55)	4.517	0.014
Gender, female%	47.50%	53.30%	77.80%	4.684	0.098
BMI	21.83(4.04)	23.11(3.90)	21.77(3.49)	0.663	0.518
Duration, months	-	-	14.24(20.05)	-	-
First episode, yes	-	-	83.30%	-	-
HAMD Somatic Anxiety	0.33(0.69)	0.60(1.18)	5.59(4.68)	31.12	< 0.001
Psychic Anxiety	0.13(0.52)	0.27(0.80)	5.18(8.01)	10.77	< 0.001
Core Depressive	0.13(0.34)	0.13(0.52)	4.06(2.93)	47.74	< 0.001
Anorexia	0.15(0.43)	0.20(0.56)	1.00(1.17)	9.38	< 0.001
HAMD Total	0.65(1.27)	1.13(2.23)	14.88(10.34)	48.39	< 0.001
HAMA HAMA Total	0.57(1.55)	1.33(2.16)	13.06(11.55)	29.56	< 0.001

Note: Data are mean (SD) or %. HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.

Table 2 Correlations between levels of leptin and clinical symptoms (HAMD and HAMA) in drug-naïve MDD group.

		HAMD					HAMA Total
		Somatic Anxiety	Psychic Anxiety	Core Depressive	Anorexia	Total	
Leptin	r Value	0.550	0.230	0.425	-0.162	0.388	0.417
	p Value	0.024*	0.374	0.089	0.535	0.124	0.095

*Correlation coefficients statistically significant at $p < 0.05$.

Figures

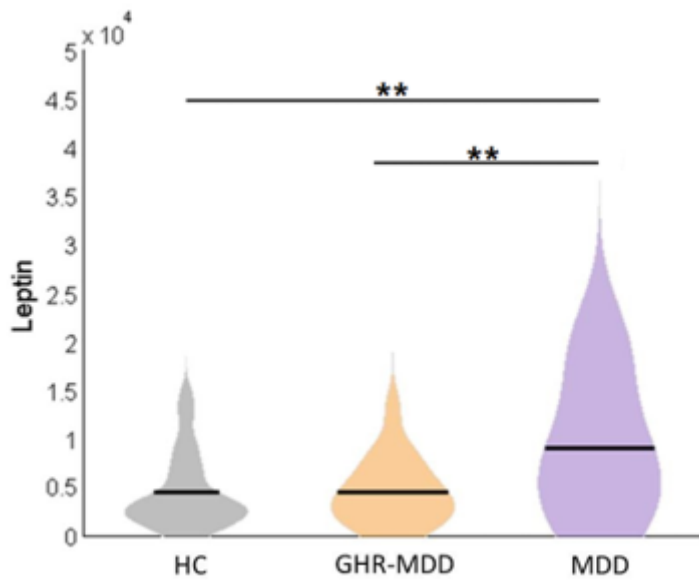


Figure 1

Comparison of plasma leptin levels by groups. Higher plasma leptin levels in drug-naïve MDD (9163.11 ± 7184.88) compared with GHR-MDD (4956.07 ± 3320.44 , $p=0.003$) and HC (4633.3 ± 3836.81 , $p=0.008$).

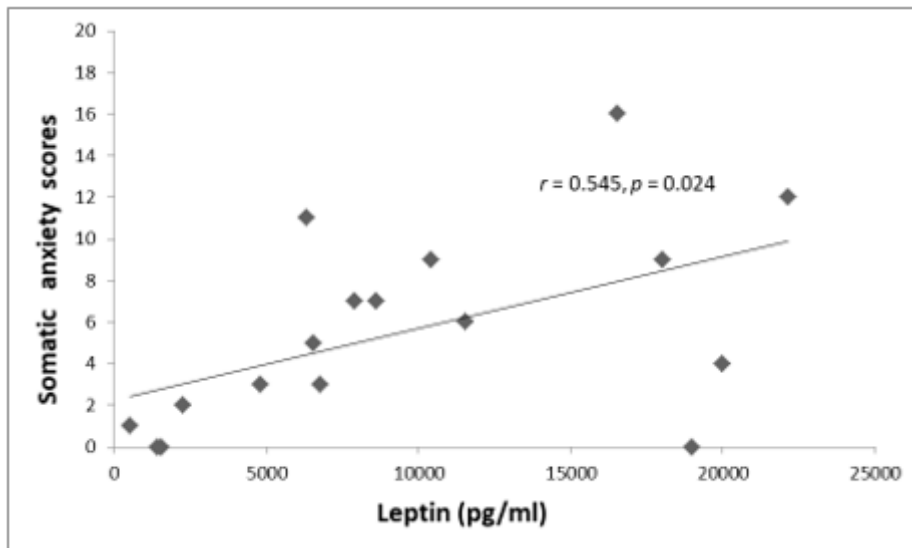


Figure 2

Spearman correlation coefficient by leptin levels and somatic anxiety scores in drug-naïve MDD. Leptin levels significantly correlated with somatic anxiety scores ($r=0.545$, $p=0.024$).

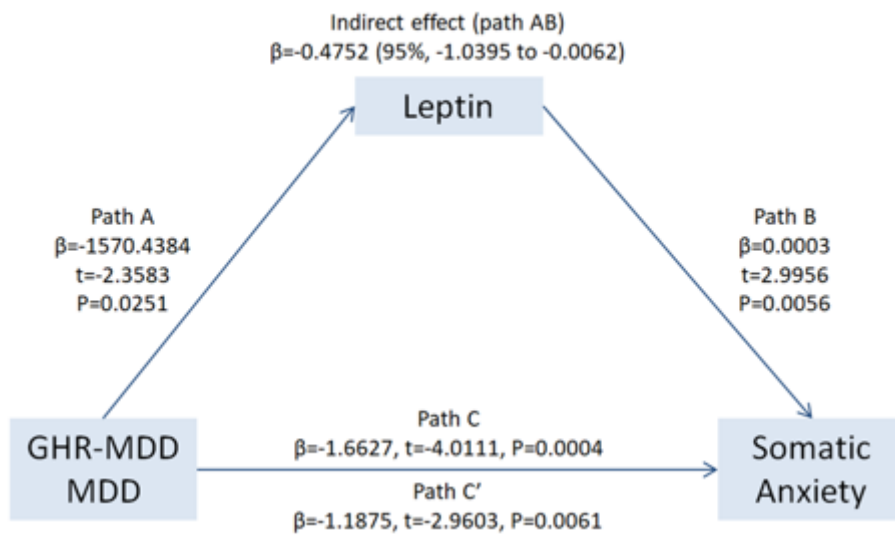


Figure 3

Leptin significantly mediated the association between diagnosis (MDD/GHR-MDD) and somatic anxiety, providing further evidence that there was an indirect way to influence patient somatic anxiety symptom by leptin. Path C represents the variance in diagnosis associated with somatic anxiety symptom, and Path C' represents the association between diagnosis and somatic anxiety symptom after taking into account leptin as a mediator. Path AB in the mediation effect and is significant at $P < 0.05$ based on confidence intervals from bias-corrected bootstrapping of 5000 samples.