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Leptin and its association with Somatic Depressive Symptoms in Patients with the Metabolic Syndrome

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Abstract

Background—This study aimed to determine the association between circulating leptin levels and total depressive symptoms as well as depressive symptom dimensions (cognitive and somatic) after controlling for important confounding factors.

Methods—The study sample was comprised of 135 participants with the metabolic syndrome. Depressive symptoms were measured using the Beck Depression Inventory - II. Leptin was measured using a leptin-specific enzyme immunoassay. Inflammation was assessed using C-reactive protein and interleukin-6 levels.

Results—Leptin was significantly associated with somatic depressive symptoms (β=0.33, *P*=0.018) but not total depressive symptoms (β=0.27, P=0.067), or cognitive depressive symptoms (β=0.21, P=0.182), after controlling for age, gender, body mass index and insulin resistance. Further adjustment for C-reactive protein and interleukin-6 levels did not alter the relationship (β=0.32, *P*=0.023) between circulating leptin levels and somatic depressive symptoms.

Conclusions—Leptin is independently associated with somatic depressive symptoms in patients with the metabolic syndrome.

Keywords

Depression; Leptin; Inflammation; Metabolic Syndrome; Blood Pressure; Body Weight; Insulin Resistance; Lipoproteins; Cardiovascular Disease

Introduction

The metabolic syndrome, a cluster of disturbances that include central adiposity, abnormal glucose regulation, dyslipidemia and elevated blood pressure (1), has been linked to cardiovascular disease morbidity and mortality (2) as well as risk for type 2 diabetes (3). The relationship between psychological factors such as depression and the metabolic syndrome has been extensively documented. Cross-sectional (4) as well as longitudinal studies (5) support an association between elevated levels of depressive symptoms and the presence of the metabolic syndrome. Similarly, a positive association between depressive symptoms and the metabolic syndrome individual components (6, 7), particularly abdominal

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Conflict of Interest Statement
The authors have no conflict of interest to disclose.

obesity (8), is well supported by the literature. Nevertheless, while the biological pathways that link the metabolic syndrome and depressive symptoms are of great interest, they are not fully understood.

Commonly associated with obesity are increased production of adipokines, chemokines, cytokines and acute phase proteins, all of which are thought to contribute to an inflammatory mileu in patients with the metabolic syndrome (9). Elevated levels of inflammatory markers have also been associated with depressive symptoms (10). A leading mechanistic hypothesis suggests that inflammation may serve as a common pathway of disease for both depression and the metabolic syndrome (11) given recent studies that show elevation of inflammatory markers, such as C-reactive protein and interleukin-6, in subjects with both the metabolic syndrome and depression after adjusting for important confounding factors (12).

A novel mechanistic hypothesis, however, has recently proposed that leptin, a peptide hormone produced primarily by differentiated adipocytes, may play an important role in the association between depression and the metabolic syndrome. This hypothesis suggests that adipose tissue is not necessarily directly implicated in the elevations of inflammatory markers. Instead, it proposes that leptin upregulates the expression of inflammatory molecules by white cells (13). In fact, leptin has recently been shown to have a role in regulating the immune response (14). Obese individuals, such as those with the metabolic syndrome, have high levels of leptin which may be responsible for the increases in inflammatory markers.

Interestingly, available data suggest that leptin may not only explain metabolic abnormalities associated with depression, but may also act as an independent marker of depression itself. Leptin has been recognized to have an influence on the dysregulation of the hypothalamic-pituitary-adrenal axis, which is a common feature among depressed individuals (15). Moreover, a possible interaction between leptin and the mesolimbic dopaminergic pathway has been proposed (16). Taken together, these preliminary research findings support a potential role of leptin as an underlying mechanistic pathway in the association between depression and the metabolic syndrome above and beyond the effects of inflammation. However, studies assessing the potential role of leptin are still lacking.

The current study aimed to determine the association between circulating leptin levels and total depressive symptoms as well as depressive symptom dimensions (cognitive and somatic) after adjusting for age, gender, insulin resistance, body mass index, and inflammation in a sample of patients with the metabolic syndrome.

Methods

Study sample

Subjects included 135 low income predominantly Hispanic participants, 64 men and 71 women (not pregnant or nursing) who meet the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome, which requires at least three of the following components: (1) central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female); (2) dyslipidemia: triglyceride ≥ 1.7 mmol/L (150 mg/dl); (3) dyslipidemia: high-density lipoprotein cholesterol < 1.0 mmol/L (40 mg/dL, male), < 1.3 mmol/L (50 mg/dL, female); (4) elevated blood pressure ≥ 130/85 mmHg; (5) glucose intolerance ≥ 6.1 mmol/L (100 mg/dl). Participants were aged 25–70 years and were excluded if they had type 1 or type 2 diabetes (known diabetes or diagnosed by Oral Glucose Tolerance Test criteria) or established cardiovascular disease; uncontrolled hypertension (systolic blood pressure>160 and diastolic blood pressure>100 mmHg); established liver disease; renal insufficiency (men; serum creatinine >1.5 mg/dl: women;

serum creatinine >1.4 mg/dl); psychiatric illness sufficient to impair full participation; chronic substance abuse in the past 5 years; endocrinopathy; neoplastic disease; chronic, systemic infectious or inflammatory disease; physical disability sufficient to impair full participation; chronic obstructive pulmonary disease or severe asthma; bariatric surgery or bowel resection; or current use of medication for weight loss. All participants were part of a larger National Heart, Lung, and Blood Institute funded study (CHARMS). The goal of the CHARMS study was to examine the effects of a structured lifestyle intervention program in patients with the metabolic syndrome.

Measures

All procedures were approved by the University of Miami Institutional Review Board. All data were collected from participants during their baseline assessment visit. During this visit, demographic information as well as anthropometric measurements such as height, weight, and waist circumference were obtained. Fasting blood samples were also drawn from participants after a 12-hour fast during the early hours of the morning and following an Oral Glucose Tolerance Test at 30, 60 and 120 minutes.

Depression—Depression was measured using the Beck Depression Inventory-II. The Beck Depression Inventory-II can be separated into two subscales, the cognitive and somatic subscales. Both cognitive and somatic scores were calculated.

Adiposity—Participant's height and weight were assessed during the baseline visit. Total adiposity was measured using the body mass index calculation (mass kg/height in m^2). Central adiposity was estimated by measuring waist circumference. Waist circumference was measured in centimeters at the midpoint between the upper iliac crest and lower costal margin at the midaxillary line.

Biochemical Markers—All biomarkers were measured in serum or plasma obtained from participants after a 12-hour fast during the early hours of the morning by standard venipuncture methods. Leptin was measured by specific enzyme-linked immunosorbent assay (ELISA; Mercodia, Winston Salem, NC). Interleukin-6 was measured by a high sensitivity ELISA (R&D Systems Inc, Minneapolis, MN). Glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, insulin and C-reactive protein were measured on a Roche Cobas 6000 analyzer (Roche Diagnostics, Indianapolis, IN) with reagents from the manufacturer. Low-density lipoprotein cholesterol was calculated by the Friedewald equation. All manufacturers' protocols were followed without modification.

Insulin resistance—Insulin resistance was calculated using the homeostasis model assessment and the insulin sensitivity index (17). The homeostasis model assessment is based on fasting insulin and fasting glucose levels (18). The insulin sensitivity index uses fasting (0 min) and 120 min post-oral glucose insulin and glucose concentrations (17).

Statistical Analysis

Preliminary statistical analyses included descriptive statistics (e.g. median and interquartile ranges) for demographic, biological and behavioral variables, outlier detection, and assessment of normality of distributions. Circulating leptin, C-reactive protein and interleukin-6 levels were found to have a non-normal distribution and were log-transformed. Participants with C-reactive protein levels greater than 10 mg/L were excluded from the analysis, as these values are likely a sign of infection. Sensitivity analyses were performed on extreme outliers. The t-student test and the Mann-Whitney U-test were used as appropriate to compare men and women on continuous demographic, biological and behavioral variables. The chi-square test of independence was used to test differences in

categorical variables. SPSS version 18.0 was used for data preparation and descriptive analysis. Multiple linear regression analyses were used to test the association between circulating leptin levels and depressive symptoms. Separate models were fitted using Beck Depression Inventory-II total score, cognitive score and somatic score as three different outcome variables. Full information maximum likelihood was used for the estimation of parameters in the presence of missing values (C-reactive protein missing values=18). Unlike older missing data procedures, such as listwise deletion, which have been shown to perform poorly, full information maximum likelihood is based on sound theory and produces efficient and accurate measures of statistical uncertainty (19). Mplus 6.0 was used for all regression analyses using full information maximum likelihood.

Results

Sample Characteristics

The study sample consisted of 135 participants (64 men and 71 women) of predominantly Hispanic descent (84.4%). Median age was 52 years. Median circulating leptin levels were 34.9 ng/ml and median Beck Depression Inventory-II total score, cognitive score and somatic score were 8, 3 and 5, respectively. When using Beck Depression Inventory-II cut-off scores to categorize participants according to symptom severity, we found 59.4% of participants fell within the minimal depression category, 21.8% fell within the mild depression category, 14.1% fell within the moderate depression category and 4.4% fell within the severe depression category.

Important demographic, biological and behavioral characteristics of the study sample are shown in Table 1. In this sample, men demonstrated higher waist circumference than women, as well as lower high-density lipoprotein cholesterol, C-reactive protein and leptin levels. Women demonstrated a higher Beck Depression Inventory-II total score and a higher somatic score, however, no difference was found in terms of the cognitive score.

Bivariate correlations among relevant biomarkers and clinical variables

Leptin was significantly correlated with C-reactive protein (r=0.46) and interleukin-6 (r=0.25). Similarly, leptin was correlated with both body mass index (r=0.50) and the insulin sensitivity index (r=−0.32). The bivariate correlations among other biomarkers and clinical variables are shown in Table 2. Sex-stratified analyses are also available as Electronic Supplementary Material (ESM; see Tables ESM1 and ESM2).

Leptin as a correlate of depressive symptoms

Leptin was strongly and significantly associated with total depressive symptoms (standardized β=0.30; P=0.000), cognitive depressive symptoms (standardized β=0.21; P=0.016) and somatic depressive symptoms (standardized β=0.39; P=0.000) in univariate analyses. In this sample, leptin alone explained 9%, 4% and 15% of the variance in total depressive symptoms, cognitive depressive symptoms and somatic depressive symptoms, respectively. Given there were significant differences by gender in depressive symptoms as well as circulating leptin, we tested the moderating effects of gender in these associations. No evidence of a gender-leptin moderation was found for total depressive symptoms (standardized β for interaction term=−0.01; P=0.995), cognitive depressive symptoms (standardized β for interaction term =−0.05; P=0.902) or somatic depressive symptoms (standardized β for interaction term =0.07; P=0.854).

In multivariate regression analyses, leptin remained significantly associated with somatic depressive symptoms (standardized β=0.33; P=0.018) but not total depressive symptoms (standardized β=0.27; P=0.067) or cognitive depressive symptoms (standardized β=0.21;

P=0.182), after adjusting for relevant confounding factors such as age, gender, body mass index and insulin resistance measured by the insulin sensitivity index (see Table 3). The multivariate model accounted for 19% of the variance in somatic depressive symptoms. Interestingly, even after incorporating cognitive depressive symptoms as a control variable in the multivariate model, we found a significant trend (standardized β=0.19; *P*=0.058) in the relationship between somatic depressive symptoms and circulating leptin levels (Table 3, Model 3). Similar results were found when using the homeostasis model assessment of insulin resistance (results not shown).

In order to elucidate specific somatic symptoms associated with elevated circulating leptin levels, we conducted a series of regression analyses using individual Beck Depression Inventory-II somatic items. After controlling for age, gender, body mass index and insulin resistance, we found a significant relationship between circulating leptin and sleep difficulties (standardized β for item 16=0.11, *P*=0.027). Similarly, a trend was found for symptoms of fatigue (standardized β for item 17=0.10, *P*=0.027) and appetite disturbances (standardized β for item 18=0.11, *P*=0.027).

The role of inflammation

Further analyses were done in order to control for inflammatory markers, C-reactive protein and interleukin-6, in the relationship between leptin levels and depressive symptoms. Somatic depressive symptoms remained significantly associated with circulating leptin levels in a model that further adjusted for C-reactive protein and interleukin-6 (standardized β=0.32; *P*=0.023). Inflammatory markers did not further explain significant variance in somatic depressive symptoms (R^2 change= 0.009, *P*>0.05). This model which included circulating leptin, C-reactive protein and interleukin-6, insulin resistance measured by the insulin sensitivity index, body mass index, age, and gender explained 20% of the variance in somatic depressive symptoms. When analyzing specific somatic symptoms associated with elevated circulating levels, we found that the association with sleep difficulties (standardized β for item 16=0.11, *P*=0.036) and appetite disturbances (standardized β for item 18=0.09, *P*=0.078) remained unaltered while the trend for symptoms of fatigue (standardized β for item 17=0.08, *P*=0.107) was further attenuated. Comparable results were found when using the homeostasis model assessment of insulin resistance (results not shown).

Finally, the relationship between circulating leptin and total depressive symptoms as well as cognitive depressive symptoms remained unaltered after adjustment for inflammatory markers C-reactive protein and interleukin-6 (results shown in Table 3).

Discussion

We report on the association between circulating leptin levels and depressive symptoms in a sample of low-income patients with the metabolic syndrome of predominantly Hispanic descent. We provide novel data assessing the potential role of leptin as a predictor of depressive symptoms while controlling for inflammation, measured by C-reactive protein and interleukin-6. Furthermore, when dividing depressive symptoms into cognitive and somatic dimensions, we found an important independent relationship between elevated circulating levels of leptin and somatic depressive symptoms, adjusting for C-reactive protein and interleukin-6, body mass index, insulin resistance measured both by the homeostasis model assessment and insulin sensitivity index, age and gender. No significant association was found between leptin and total depressive symptoms or cognitive depressive symptoms.

Previous studies have examined the potential role of leptin in depression in both animal models and humans (15, 20–22). However, most studies have aimed to study total

depressive symptoms without elucidating the symptom dimensions more commonly associated with this metabolic disturbance. The identification of depression dimensions might enhance diagnosis and treatment of depression in this population. To our knowledge, this is the first study to present evidence of an independent association between somatic depressive symptoms, as opposed to cognitive symptoms, and circulating leptin levels in both men and women adjusting for the effects of an inflammatory marker such as C-reactive protein and interleukin-6. The association between leptin levels and somatic symptoms was also independent of body mass index, insulin resistance, age and gender.

Somatic depressive symptoms include loss of energy, changes in sleeping pattern, changes in appetite, tiredness and fatigue, loss of interest in sex and irritability; whereas, cognitive depressive symptoms are characterized by sadness, pessimism, guilty feeling, self-criticalness and dislike, suicidal thoughts, loss of interest, agitation, indecisiveness and worthlessness (23). This study extends the findings of previous reports that examined somatic depressive symptoms and their relationship with inflammatory markers (24, 25) and the metabolic syndrome (12). Moreover, our results are of potential interest given recent evidence suggesting somatic symptoms may be a better predictor of risk for cardiac events than cognitive symptoms in patients with cardiovascular disease (26–33). In a study examining depressive symptom dimensions following acute coronary syndrome, for example, Roest and colleagues found that somatic symptoms were associated with disease severity and all-cause mortality at a 12-month follow-up. Similarly, a study examining health status and prospective cardiovascular prognosis found that somatic depressive symptoms were associated with poor health status (left ventricular ejection fraction, previous myocardial infarction, among others) and prospectively predicted cardiovascular mortality and cardiac events, even after adjusting for other major prognostic medical variables (26). Comparable results have been reported in patients with documented medically stable cardiovascular disease (28), chronic heart failure (32) and subclinical atherosclerosis (34).

Furthermore, when examining specific somatic symptoms associated with elevated circulating leptin, we found that changes in sleep pattern and appetite had the strongest relationships. These results are in line with previous reports on the functional role of leptin in appetite regulation and energy homeostasis (15, 35). Similarly, leptin has been implicated in the regulation and duration of sleep and recent findings indicate that depression when accompanied by sleep disturbances results in elevated leptin levels (36). Interestingly, another recent study showed that comorbid depression and sleep apnea, a highly prevalent sleep disorder in metabolic syndrome patients (37), resulted in higher risk for myocardial infarction morbidity and mortality than either condition alone (38).

In addition to examining depression as having separate somatic and cognitive symptoms dimensions, we also analyzed the relationship between total depressive symptoms and circulating leptin levels. In contrast to findings that reported a positive association between depressive symptoms and circulating leptin level, our study found a non-significant association between leptin levels and total depressive symptoms after controlling for inflammatory markers, body mass index, insulin resistance, age and gender. These results are consisted with a recent study that reported the association between total depressive symptoms and leptin was mediated by adiposity (39). Similarly, gender is an important confounding factor given that in our sample as well as other reports (20, 21, 40), women had significantly higher depressive symptoms and circulating leptin compared to men. Our results did not support, however, a leptin-gender interaction. Previous available studies have reported gender-dependent associations without formally testing for moderation (36), have not controlled for gender (13) or have been conducted in all female samples (20, 21, 40).

Other potential factors explaining the differences in results among studies may include the questionnaires used to assess depressive symptoms and/or the characteristics of the study samples in terms of body mass index and ethnicity. Whereas our study used the Beck Depression Inventory-II as a measure of depression, other studies have used the Hamilton Depression scale (40) or the depression subscale of the Hospital Anxiety and Depression Scale (22). It is possible that the Hamilton Depression Scale, the Hospital Anxiety and Depression Scale and the Beck Depression Inventory-II have different factor structures and perform differently as a tool to detect depressive symptoms that are mainly cognitive or somatic in nature. Finally, differences in terms of the study population may affect the results. Our sample was predominantly comprised of relatively low socioeconomic status U.S. Hispanics (84.4%) with the metabolic syndrome. This population may be culturally, genetically and clinically different than those previously studied. For example, Labad et al. (22) studied patients with type 2 diabetes, Pasco et al. (21) worked with a sample of women with a life-time history of major depressive disorder, Cizza and colleagues (40) studied premenopausal women, and Hafner et al. (36) studied a healthy subsample of Caucasian participants.

The mechanisms relating somatic depressive symptoms and circulating leptin levels as well as the directionality of this relationship remain unknown. Previous studies have linked depressive symptoms with unhealthy behaviors, such as increased fat intake and decreased physical activity, which promote weight gain (5, 41, 42). In fact, evidence supports a bidirectional association between obesity and depression (8). Increases in waist circumference and weight gain may, in turn, lead to elevated leptin levels. Alternatively, leptin has been shown to be involved in up-regulating the innate immune response by increasing the production of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha (14). Inflammatory cytokines have been consistently linked to depression (12, 13, 25). In this study, however, we found a significant relationship between leptin levels and somatic depressive symptoms even after controlling for both body mass index and inflammatory markers, suggesting the mechanistic pathways are likely to be multiple. Other hypotheses include possible interactions between leptin signaling and the mesolimbic dopamine pathway (43), a possible neurotrophic action of leptin (44), and the hypothalamic-pituitary-adrenal axis hypothesis (15, 45). This hypothesis, derived from research in animal models, suggests leptin has the capacity to regulate the hypothalamic-pituitary-adrenal axis (15, 46). Accumulating evidence so far indicates that hypothalamic-pituitary-adrenal axis dysregulation is a common feature among depressed individuals (15). Furthermore, research suggests that leptin receptors may have a more important role in depression than circulating leptin. Two recent studies (47, 48) suggest leptin receptor signaling in the hippocampus is essential for mood regulation. These researchers showed selective deletion of leptin receptors in the adult hippocampus induces depression-like behaviors in mice (47, 48).

Further research is needed to clarify the mechanistic pathways involved in this relationship and to elucidate the directionality of the association with the use of longitudinal research. This may have importance since it is possible that interventions, both psychotherapeutic and pharmacological, aimed at reducing somatic symptoms could have an impact on circulating leptin among men and women in this population. Although these issues for future investigation are important, we believe that our findings also have an immediate application, given that depression (a treatable factor) appears to play a role in the metabolic syndrome and thus, is an important factor to consider in the design of metabolic syndrome prevention strategies.

A strength of this study is the inclusion of predominantly U.S. Hispanic participants with the metabolic syndrome. Hispanics, the fastest growing minority in the United States, have been

found to be at particular disadvantage when it comes to the prevalence of the metabolic syndrome (49). Yet Hispanics are still understudied in relation to both cardiovascular disease and mental health.

This study is limited by its relatively small sample size. A larger sample will result in increased statistical power to detect associations between variables of interest. Similarly, our study sample is representative of a small subset of individuals with the metabolic syndrome without any additional chronic condition (such as uncontrolled hypertension or diabetes). An epidemiological study that includes a population based sample of participants would provide informative data regarding the generalizability of these results. The present study was also limited by the use of body mass index as a proxy measure of adiposity. More direct measures of percept body fat such as dual-energy x-ray absorptiometry (DXA) provide a better characterization of body adiposity and should be considered in future studies. Finally, given the cross-sectional nature of our study, the direction of the relationships between C-reactive protein, leptin and depressive symptoms cannot be determined. However, pending prospective data, our findings provide important insights into the relationship between the metabolic syndrome and depression and the possible underlying mechanistic pathways linking these conditions.

Conclusions

In summary, we found an independent relationship between elevated circulating levels of leptin and somatic depressive symptoms, adjusting for inflammation measured by C-reactive protein and interleukin-6, body mass index, insulin resistance measured both by the homeostasis model assessment and the insulin sensitivity index, age and gender. No significant association was found between leptin levels and total depressive symptoms or cognitive depressive symptoms after controlling for potential confounding factors. Further research is needed to elucidate the complex pathways linking depression and the metabolic syndrome while incorporating the potential role of leptin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic, biological and behavioral characteristics of the study sample

	Median (IQR)			*P* value
	Total Sample (n=135)	**Men (n=64)**	**Women (n=71)**	
Education, years	12 (11–15)	13 (12–16)	12 (11–15)	0.085
Income > 20 000 US.D, %	30.0	26.0	32.0	0.262
Ethnicity, %				0.284
Caucasian	4.5	7.0	1.6	
African American	10.4	11.3	9.5	
Hispanic	84.4	81.7	88.9	
Age, years	52 (45–58)	50 (42–58)	53 (47–58)	0.077
Body Mass Index, kg/m	32.3 (29.9–35.1)	32.0 (29.4–33.9)	32.6 (30.1–35.6)	0.097
Waist Circumference, cm	104 (99–110)	108 (103–114)	102 (97–106)	**<0.001** *
Triglycerides, mg/dL	194 (150–240)	205 (163–255)	188 (147–233)	0.271
LDL Cholesterol, mg/dL	124.0 (102.2–146.8)	122.6 (95.9–141.4)	125.0 (108.1–154.5)	0.131
HDL Cholesterol, mg/dL	38 (33–44)	34 (31–38)	41 (37–47)	**<0.001** *
C-Reactive Protein, mg/L	3.1 (2.0–5.7)	2.2 (1.4–3.6)	4.0 (2.8–6.2)	**<0.001** *
Interleukin-6, pg/mL	2.0 (1.4–3.1)	1.8 (1.2–3.0)	2.3 (1.6–3.1)	0.062
Leptin, ng/mL	34.9 (18.5–53.5)	18.9 (13.0–27.4)	45.6 (37.4–83.6)	**<0.001** *
Homeostasis Model Assessment	2.7 (2.0–3.9)	2.5 (2.0–3.8)	2.7 (1.9–4.1)	0.795
Insulin Sensitivity Index	1.3 (1.1–1.8)	1.3 (1.1–1.9)	1.3 (1.1–1.7)	0.611
BDI-II Total Score	8 (4–16)	6 (3–11)	10 (5–17)	**0.010** *
BDI-II Cognitive	3 (1–8)	2 (1–6)	4 (1–9)	0.183
BDI-II Somatic	5 (2–7)	3 (2–6)	6 (3–8)	**<0.001** *

* $P<0.05$,

BDI-II= Beck Depression Inventory-II

Table 2

Pearson correlations of biomarkers and clinical variables included in regression models

	Biomarkers and Clinical Variables							
	Leptin	**CRP**	**IL-6**	**BMI**	**ISI**	**BDI-T**	**BDI-C**	**BDI-S**
Leptin	1							
CRP	0.457**	1						
IL-6	0.253**	0.298**	1					
BMI	0.497**	0.280**	0.149	1				
ISI	−0.318	−0.267	−0.104	−0.297	1			
BDI Total	0.292**	0.191*	0.108	0.176*	−0.085	1		
BDI Cognitive	0.202*	0.136	0.094	0.138	−0.051	0.962**	1	
BDI Somatic	0.383**	0.245**	0.109	0.205*	−0.121	0.892*	0.735**	1

*$P<0.05$,

**$P<0.01$,

CRP=C-reactive protein, IL-6=interleukin-6, BMI=body mass index, ISI= insulin sensitivity index, BDI=Beck Depression Inventory II

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Table 3

Leptin and its association with total, cognitive and somatic depressive symptoms

	BDI-II TOTAL		BDI-II COGNITIVE		BDI-II SOMATIC	
	β (95% CI)	***P* value**	**β (95% CI)**	***P* value**	**β (95% CI)**	***P* value**
Model 1						
Age	0.17 (0.03–0.31)	0.049	0.12 (−0.03–0.26)	0.181	0.22 (0.09–0.35)	0.018
Gender	0.01 (−0.2–0.22)	0.932	0.03 (−0.19–0.24)	0.838	−0.02 (−0.22–0.18)	0.873
Body Mass Index	0.04 (−0.13–0.21)	0.679	0.04 (−0.13–0.22)	0.688	0.04 (−0.13–0.2)	0.707
Insulin Sensitivity Index	0.04 (−0.12–0.19)	0.707	0.03 (−0.13–0.2)	0.733	0.04 (−0.11–0.18)	0.695
Leptin (log)	0.27 (0.03–0.52)	0.067	0.21 (−0.05–0.46)	0.182	**0.33 (0.1–0.56)**	**0.018** *
R square	0.113	0.030 *	0.058	0.142	0.188	0.002 *
Model 2						
C-reactive Protein (log)	0.07 (−0.1–0.24)	0.519	0.04 (−0.14–0.22)	0.717	0.10 (−0.06–0.26)	0.304
Interleukin-6 (log)	0.02 (−0.13–0.17)	0.822	0.04 (−0.12–0.19)	0.698	−0.01 (−0.15–0.13)	0.893
Leptin (log)	0.26 (0.02–0.51)	0.082	0.20 (−0.06–0.46)	0.208	**0.32 (0.09–0.56)**	**0.023** *
R square	0.119	0.025 *	0.063	0.126	0.197	0.001 *
Model 3						
BDI-II symptom dimension	-	-	0.78 (0.71–0.86)	<0.001 *	0.67 (0.60–0.74)	<0.001 *
Leptin (log)	-	-	−0.05 (−0.23–0.13)	0.641	0.19 (0.03–0.35)	**0.058**
R square	-	-	0.553 †	<0.001 *	0.616 ††	<0.001 *

* *P*<0.05;

BDI-II=Beck Depression Inventory; Models 2 and 3 controlled for age, gender, body mass index, insulin sensitivity index;

† controlled for Beck Depression Inventory-II Somatic,

†† controlled for Beck Depression Inventory-II Cognitive