

ORIGINAL ARTICLE

Decreased Levels of Fasting Serum Leptin in Patients With Schizophrenia: A Case-Control Study

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Abstract

Objective: Evidence suggested that leptin may be implicated in the pathophysiology of metabolic disruptions in schizophrenia. The findings of the leptin in patients with schizophrenia have been inconsistent. The aim of this study was to evaluate fasting leptin in the patients with schizophrenia and the association with leptin levels and gender, BMI, clinical variables such as psychopathology scores, suicidal behaviour and type of medication.

Methods: Forty-eight patients with schizophrenia and 36 age-gender-BMI matched healthy controls (HC) were assessed. We collected venous blood samples in the morning and serum leptin were measured using the ELISA kit.

Results: The levels of fasting leptin were significantly decreased in patients with schizophrenia compared with the HC ($P=0.021$), also after adjusting for confounders ($P=0.009$). In the regression analysis, being female ($\beta=-0.51$, $t=-3.458$, $P<0.001$) and higher BMI ($\beta=3.675$, $t=3.675$, $P<0.001$) were found significant predictor to higher level of the fasting leptin and we did not observe a relationship between fasting level of leptin and age, smoke status, cumulative antipsychotic use, clinical status and having suicidal attempt in patients with schizophrenia.

Conclusion: The exploratory study detected decreased fasting leptin levels and significant relationships between higher leptin levels and gender and BMI in the stable medicated patients with schizophrenia. Future studies are considered the role of adipose tissue related pathways and gender differences to understand the underlying mechanisms of metabolic disruptions in patients with schizophrenia.

Keywords: Leptin, Schizophrenia, Adiposity, BMI, Gender

INTRODUCTION

The percentage of metabolic complications is increased in patients with schizophrenia (1). Similarly, epidemiological studies estimate that metabolic syndrome is almost two times more prevalent (2) and type 2 diabetes is up to three times higher in patients with schizophrenia (3, 4). Recent meta-analyses have showed that the cardiac abnormalities contribute to increase the premature mortality (5) and the life expectancy seems to be substantially lessened over time among people with schi-

zophrenia (6). The processes underlying these metabolic changes and higher mortality rates are still scarce and not understood yet.

Some evidence suggested that leptin might have a function in the pathophysiology of schizophrenia (7). Leptin, a cytokine-like molecule, is synthesized in white adipose tissue and plays a significant role in the regulation of appetite, long-term management of energy balance and body weight (8). Leptin can cross to the blood-brain barrier and reach into the brain tissue and binds into the leptin receptors of hypothalamus in the arcuate nucleus and feed the information about the status of the body energy stores (9). Leptin deficiency causes extreme obesity and can lead to cardiovascular complications (10). Leptin was shown to play an essential part in the negative feedback against dopamine (D2) receptor activity (11, 12) which may be connected to

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positive symptoms of schizophrenia. Furthermore, leptin can regulate to the regulation of the mesolimbic dopaminergic system and influence the mechanisms of food intake and reward signalling. The interaction between leptin and the dopaminergic system may reveal a potential target for therapeutic options in patients with schizophrenia (7).

Preclinical and clinical studies (13) have supported the relationship between leptin dysregulation and clinical psychopathology in patients with schizophrenia (14). Previously studies have found higher leptin levels in medicated patients with schizophrenia (7). Also, some studies reported decreased leptin levels in patients with schizophrenia particularly in patients who had suicide attempts (15, 16). A recent study confirmed that the association between the decreased level of leptin and depressive symptoms in patients with chronic schizophrenia and suggested that leptin, as a potential biomarker of lipid-regulation, might be considered in suicide research (14). There are also some reports which have found no difference (17, 18) in leptin levels in patient with schizophrenia compared to healthy controls. Regarding the current literature, it is possible that confounding factors, such as the time of blood sampling co-morbid metabolic diseases, could also explain the heterogeneity on the levels of leptin in patients with schizophrenia (7).

Our study aims to investigate: (1) whether plasma leptin levels were altered in patients with schizophrenia compared to the healthy controls despite adjusting for gender, age and BMI; (2) whether there was a relationship between fasting level of leptin and demographic and psychopathological parameters such as symptom clusters and suicidal attempts.

METHODS

Patients

We recruited forty-eight clinically-stable patients diagnosed with schizophrenia spectrum disorders according to the DSM-V criteria from the Bezmialem Vakif University, Department of Psychiatry in Istanbul, Turkey. The Positive and Negative Syndrome Scale (PANSS) was used and age of all participants aged between 18 and 65. We recruited patients with schizophrenia who had no acute psychotic episode, no change in medication dosage in the past year to our study. All patients were on the antipsychotics at the time of blood draw with a cumulative chlorpromazine equivalent dose (CPZe)

(mean: 770.10 ± 456.68). The antipsychotics that patients were taking at the time of enrolment were; clozapine (n=12, %25), olanzapine (n=8, %17), risperidone (n=26, %54), quetiapine (n=17, %35), haloperidol (n=3; %0.06), amisulpride (n=13, %27), aripiprazole (n=10, %21), typical long acting injection (n=15, %31), atypical long acting injection (n=16, %33). The antidepressant (SSRI) that patients were taking at the time of enrolment was (n=21, %44).

Healthy Controls

We enrolled matched thirty-six healthy controls (HC) regarding to age, gender, BMI, and smoking status in this study. The exclusion criteria for HC were a personal and family history of schizophrenia, bipolar disorders, severe major depressive disorders, and obsessive-compulsive disorder.

We excluded the patients and HC from the study based on having learning disabilities, dementia, substance abuse or dependence, history of head trauma, being shift worker, having a chronic systemic disease, epilepsy, and use of hormone treatments including oral contraceptives, pregnancy within the previous 12 months.

The Medical Ethical Review Committee of the Bezmialem Vakif University approved the study, which was conducted according to the latest version of the Declaration of Helsinki. Written informed consent was taken from all participants.

The Positive and Negative Syndrome Scale

The PANSS is a 30 – item clinician-rated scale and include 3 subscales for the positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). The items are ranging from 1 to 7 as an absent to extreme severity.

Enzyme-Linked Immunosorbent Assay (ELISA)

We collected blood samples into BD Vacutainer®, UK tubes, after 12 h of fasting, between 8.00 and 9.00 am. Blood samples were centrifugated (10 min at 2,500 x g, 4°C) and stored at –80°C until use. The Human Leptin levels were measured with ELISA using commercial kits and an ELISA reader. Anti-Leptin antibodies 96-well ELISA plates. Then biotinylated detection antibody specific for LEP and Avidin-Horseradish Peroxidase (HRP) conjugate was added to each micro plate and incubated. Free component was washed away. The absorbances were read at 450 nm in a microplate reader and then the Human Leptin concentrations were calculated according

to the standard curve. The results were showed in pg/ml. Sensitivity: the minimum detectable dose of Human Leptin was 46,88 pg/mL and detection range were 78,13-5000 pg/mL.

Statistical Analysis

SPSS was used for statistical analysis (Macintosh version 22.0). The distribution of data was detected by the Kolmogorov–Smirnov test. Sociodemographic variables were calculated by Chi-square tests for categorical variables and T-test for continuous variables. Levels of leptin were compared in schizophrenia and HC groups using ANCOVA, also adjusted for the age, gender, and BMI. The patients with schizophrenia and HC were evaluated separately with the regression analysis. The fasting serum leptin levels were regressed on the participants' age, gender, BMI, smoke status, antipsychotic use (CPZe), clinical status (PANSS score) and having suicidal attempt which has been found associated with the level of leptin in the current literature in patients with schizophrenia. Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows demographic variables and the groups differed regarding to the marital status.

Table 1. Demographic comparisons between the patients with schizophrenia and healthy controls

	SZ (N:48)	HC (N:36)	t / Chi-square	p
Age (mean ± SD)	42.35±10.74	39.02±11.12	t= 1.387	.169 ^{NS}
Female (%)	% 37.5 (18/48)	% 50 (18/36)	$\chi^2 (1) = .302$.377 ^{NS}
Marital Status (Single (%))	%82.2 (37/45)	%35.1 (13/36)	$\chi^2 (4) = 18.920$	<0.001
BMI (mean ± SD)	27.35±4.49	26.78±4.70	t= 1.236	.231 ^{NS}
Smoking (Yes (%))	%52.3 (23/41)	%50 (18/36)	$\chi^2 (2) = .041$.840 ^{NS}

SZ= Patients with schizophrenia; HC= Healthy controls; BMI= Body-mass Index

Sociodemographic variables were calculated by Chi-square tests for categorical variables and T-test for continuous variables. The significance threshold was set at .05.

Clinical characteristics and treatment options summarized in Table 2.

Table 2. Clinical characteristics of the patients with schizophrenia

Duration of illness (mean ± SD)	18.70±9.86
Age of onset (mean ± SD)	23.75±8.19
Number of Hospitalization (mean ± SD)	2.50±2.32
Number of relapses (mean ± SD)	5.14±3.14
Suicide attempt (Yes (%))	(23/48) %48
PANSS-Global (mean ± SD)	32.70±6.59
PANSS-Positive (mean ± SD)	15.10±6.36
PANSS-Negative (mean ± SD)	18.56±6.49
Combined antipsychotic treatment (Yes (%))	(38/48) %79
Antidepressant (Yes (%))	(21/48) %44
PANSS= Positive and Negative Symptom Scale	

The Group Differences in Fasting Serum Leptin Concentrations

The mean serum fasting leptin level for the patients with schizophrenia was 3732.41± 2058.31 pg/mL and for the healthy controls was 4805.02±2083.53 pg/mL. The mean serum fasting leptin level was significantly lower in patients with schizophrenia than in HC ($t = 2.36$, $p = 0.021$). (Fig. 1)

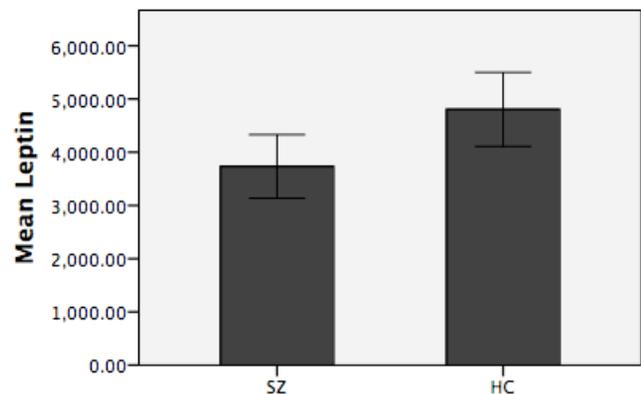


Figure 1. Serum fasting leptin concentrations in patients with schizophrenia (SZ) and healthy controls (HC)

The fasting serum level of leptin ($F = 7.17$, $p = 0.009$, $N2 = 0.082$) stayed significantly lower in schizophrenia group than in healthy controls after adjusting cofounders such as age, gender, BMI by using one-way analysis of covariance.

Fasting Leptin Levels Regarding to Antipsychotic Treatment and in Healthy Controls

There are not enough valid cases to perform the Kruskal-Wallis Test for treatment groups. Descriptive statistics are computed and summarized in Figure 2.

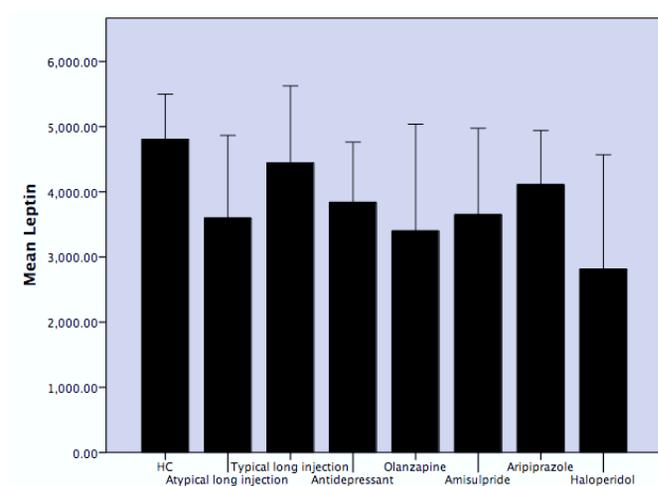


Figure 2. Fasting leptin levels regarding to class of medications in patients with SZ and in healthy controls

Regression Analysis on Fasting Serum Level of Leptin in Patients with Schizophrenia and Healthy Controls

The patients with schizophrenia and HC were analysed separately. The fasting serum leptin levels were regressed on the participants' age, gender, BMI, smoke status, antipsychotic use (CPZe), clinical status (PANSS score) and having suicidal attempt which has been found associated with the level of leptin in the current literature in patients with SZ. In patients with SZ, being female and having higher BMI were found to be related with a higher level of the fasting leptin (Table 3).

Table 3. Regression analysis on fasting serum level of leptin in patients with schizophrenia

	B	SE	β	t	p
Age	-11.42	23.88	-.060	-.478	.635
^a Gender	-2164.06	625.82	-0.51	-3.458	.001
BMI	168.53	45.86	.457	3.675	.001
^b Smoke	696.19	575.45	-.060	1.210	.234
^c Suicide	-132.66	533.65	-.033	-.249	.805
PANSS-Global	-.004	54.26	.004	.022	.982
PANSS-Negative	-7.75	43.99	-.024	-.176	.861
PANSS-Positive	29.62	48.97	.089	.605	.549
CPZe	0.84	0.60	.188	1.400	.170
^d Antidepressant	45.576	488.85	.011	.093	.926

B = Unstandardized beta coefficient; SE = Standard error; β = Standardized beta coefficient; PANSS=Positive and Negative Symptom Scale; CPZe=Chlorpromazine Equivalent Dose; BMI=Body-mass Index

^aGender: 0 = Female; 1 = Male.

^bSmoke: 0 = No; 1 = Yes.

^cSuicide: 0 = No; 1 = Yes.

^dAntidepressant: 0 = No; 1 = Yes.

The fasting level of leptin were regressed on the participants' age, gender, BMI in HC. Age ($B = -60.541$, $SE = 21.165$, $\beta = -.336$, $t = -2.860$, $p = 0.008$), gender ($B = -2363.225$, $SE = 456.376$, $\beta = -.590$, $t = -5.178$, $p < .001$) were found to be predictor variables and BMI was found trend to significant predictor ($B = -93.077$, $SE = 46.253$, $\beta = .219$, $t = 2.012$, $p = 0.057$) in the regression model.

DISCUSSION

The main objective of the study was to compare fasting serum leptin levels between in patients with schizophrenia and healthy controls after adjusting for major confounding factors. The main results of our study were that patients with schizophrenia had decreased levels of fasting serum leptin compared with the healthy controls after adjusting confounders and the higher fasting leptin concentrations were related to higher BMI and being female in patients with schizophrenia.

Our finding on leptin levels is in line with the previous studies, which showed decreased level of leptin has reported in patients with schizophrenia (15, 16). However, contrary to our findings, some studies showed no difference on leptin levels in patients with SZ (17, 18). Furthermore two meta-analyses showed increased leptin levels in patients with schizophrenia compared with healthy controls (7, 19) and one of the meta-analysis suggested that the increased level of leptin and the induced-weight-gain might be a consequence of antipsychotic-induced leptin-resistance status (19). However, conflicting results have been obtained in antipsychotic-free or naïve patients with schizophrenia, where increases, decreases or non-differences in leptin levels have found compared with healthy controls (7, 20). Moreover, recently, a meta-analysis of hormones of appetite pathways including leptin in patients with first-episode psychosis was conducted with 31 eligible studies and found the elevated insulin levels and decreased leptin levels even before the antipsychotic treatment (21). We collected all blood samples after 12 h of fasting between 8.00-9.00 am and took account for having another metabolic disease as an exclusion criterion for all participants in our study. Hence, the lack of control of confounder factors might explain the observed heterogeneity of the results of leptin levels in patients with schizophrenia.

We found that BMI in patients with schizophrenia moderated the level of leptin in our sample. Our result is in parallel to recent studies (14, 20) and a meta-analysis showed that longitudinal variations in leptin

levels participants with schizophrenia were related to increases in BMI (19). The alterations of leptin in patients with schizophrenia suggested that might occur a result of weight gain rather than a direct impact of atypical antipsychotic use on leptin physiology (22). Furthermore, the observed association between leptin and inflammatory, lipid markers support the hypothesis that metabolic changes are occur before the chronic phase of disease (20) and the interaction between adiposity and inflammation has been linked to leptin in patients with schizophrenia and depression (14).

We have found that female patients with schizophrenia and healthy controls are prone to having increased leptin levels. Our finding is strongly supported with current literature, for example in a meta-analyses with 27 cross-sectional studies suggested that leptin levels are higher in females compared with males patients with schizophrenia (7). The gender differences of the leptin suggested for females have a higher range of adipose tissue and the origination rate of leptin per unit mass of adipose tissue than males (23). Secondly, Martorell et al. (20) have proposed that there might be some specific associations between leptin and food consumption, which may be related only in females.

We did not find any association between the fasting serum leptin levels and cumulative antipsychotic dosage, PANSS scores, having suicidal attempt and antidepressant treatment which have been proposed in the current literature that these variables might be linked with the level of leptin in patients with schizophrenia. Some studies suggested that the decreased levels of leptin were associated with a high risk of suicidal behaviour and depressive symptomatology in schizophrenia spectrum patients (14, 15). One study showed that leptin has associated with PANSS positive and total scores (17) and another one showed that significant negative association between leptin levels and the depressing factor scores on the PANSS (24). The last meta-analysis of 27 cross-sectional studies stated that they could not evaluate the relation with levels of leptin and psychopathology in schizophrenia for lack of data in studies (7) our findings are in line with this analysis.

Our study is current exploratory research with the moderately small sample size requires further confirmation in further large-scale longitudinal studies. We did not find evidence of a significant difference in medication classifications for not enough valid cases for each treatment group to perform the statistics. The descriptive analysis summarised as a figure, future studies should consider the sample size of the studied

population to explore the treatment effect on fasting leptin level. The consideration of lifestyle factors (dietary intake, physical activity) has been proposed that might impact circulating leptin levels. Therefore, future studies should account for total body fat, percentage of body fat and fat distribution and lipid profile of the participants.

Schizophrenia has been associated with altered endocrine functions (25) and the high prevalence of endocrine disruptions may play a role in the pathogenesis of cardiometabolic abnormalities in schizophrenia (4). Future studies should consider adipose tissue and lipid-related pathways and gender to clarify the alteration of metabolic changes in patients with schizophrenia. Some specific lifestyle or adipose tissue factors may be related with the level of leptin in female patients with schizophrenia.

Ethics Committee Approval: This study approved by the Clinical Trials Ethics Committee of Bezmialem Vakif University, 13 Sep 2017, 18/9

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