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Serum Leptin and Cholesterol Levels in Patients with Bipolar Disorder

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Key Words
Leptin · Cholesterol · Manic episode · Bipolar disorder

Abstract
Low cholesterol levels have been reported in patients with manic episodes. Leptin seems to be strongly associated with lipid metabolism. In the present study, therefore, serum total cholesterol and leptin levels were compared in 16 patients with manic episodes, 16 with bipolar I disorder in full remission and 16 healthy controls. The serum total cholesterol and leptin levels were measured and Young Mania Rating (YMRS) and Hamilton Depression Rating Scales (HAM-D) were administered for each subject. Both the patients with manic episodes and the patients with bipolar I disorder in full remission had markedly low serum cholesterol and leptin levels compared with controls, though the difference was more obvious in patients with manic episodes. In addition, there were negative correlations between YMRS scores and serum cholesterol or leptin levels in the patients with manic episodes. Our results suggest that the patients with manic episodes and those with bipolar I disorder in full remission seem to be associated with decreased serum cholesterol and leptin levels.

Introduction

Low cholesterol values have been associated with the expression of aggressive and impulsive behavior in a variety of psychiatric disorders, e.g. intermittent explosive disorder [1] and antisocial personality disorder [2]. In depressed patients, low [3, 4] and high [5] cholesterol levels compared with healthy controls have been found. Likewise, low cholesterol levels have been reported in patients with manic episodes [6].

Leptin is an adipocyte hormone discovered by Zhang et al. [7] as the product of the *ob* gene. The main role of leptin in metabolic homeostasis is regulating food intake and energy expenditure, providing the hypothalamus with information on the amount of body fat [8]. Recently, a growing number of studies have focused on leptin levels in psychiatric disorders and psychotropic drug use [9–14]. A positive correlation has been shown between serum leptin concentration and total cholesterol, triglyceride or the percentage body fat [15]. Furthermore, an interaction between leptinergic and serotonergic systems in the central nervous system has been demonstrated [16]. Diminished serotonergic neurotransmission has been implicated in manic episodes. Low serotonin activity has been discussed to be the reason for many behavioral abnormalities, such as suicide attempts, appetite changes, agressivi-

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ty, and sleep disturbance, some of which generally occur in bipolar patients [17]. Leptin regulates food intake [18], sexual behavior [19] and locomotion [20], and interacts with sleep-wake regulation [21]. Therefore, we decided to measure serum total cholesterol and leptin levels in patients with manic episodes, or bipolar I disorder in full remission and in healthy controls, as manic episodes are characterized by change in food intake, sleep-wake regulation, locomotion and sexual behavior.

Methods

Subjects and Design

The study consisted of 32 patients (aged 18–43 years) who applied to the Firat University School of Medicine, Department of Psychiatry and were diagnosed with manic episode (n = 16) and age- and sex-matched patients with bipolar I disorder in full remission (n = 16) according to DSM-III-R criteria. Twenty or greater scores on the Young Mania Rating Scale (YMRS) [22] were necessary for patients with manic episodes, while 12 or less YMRS scores were required for patients with bipolar I disorder in full remission.

Each patient underwent a detailed diagnostic evaluation by a trained psychiatrist by using the Structured Interview for DSM-III-R (SCID) [23]. The patients with any kind of axis I comorbidity were excluded. All subjects were drug-free for at least 2 weeks. All subjects were assessed by the 21-item Hamilton Depression Rating Scale (HAM-D) [24] and the YMRS. Exclusion criteria included the presence of a severe physical illness, a history of alcohol and substance abuse or dependence, a previous history of cholesterol lowering treatment, the presence of any endocrinological state and treatment with any psychotropic medication within the last 2 weeks. All participants were carefully assessed to rule out autoimmune, pulmonary, infectious diseases and neoplasms. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by the squared height (in meters) (BMI = kg/m^2).

Available 16 healthy controls according to the exclusion criteria were chosen among the staff members. Controls were interviewed with the nonpatient version of the SCID (SCID-NP) [25] to exclude any axis I disorder.

Written informed consent to participate in the study was obtained from the subjects after they had been thoroughly informed about the research details. The research protocol was approved by the Local Ethics Committee of the Firat University School of Medicine.

Determination of Serum Leptin and Total Cholesterol

The patients and controls fasted overnight. Venous blood samples were drawn from the antecubital vein at 08.00 a.m. to determine the serum levels of leptin and cholesterol. The leptin levels were measured using the DRG Diagnostics kit (DRG Instruments GmbH, Germany) with the enzyme-linked immunosorbent assay method. The limit of detection was 0.2 ng/ml. Total cholesterol levels were assayed using a Randox total cholesterol kit (Randox Laboratories Ltd., UK) and an Olympus AU 600 autoanalyzer (Olympus Corp., Japan).

Statistical Analysis

Statistical analysis was performed by the statistical package for social sciences (SPSS/PC version 9.05, 1998). In the statistical analysis, analysis of variance and Pearson's correlation test were used. The General Linear Model command of the SPSS was used when controlling for covariates. Differences were considered significant at $p < 0.05$ for all these tests.

Results

The characteristics of the subjects are summarized in table 1. As shown in table 1, there were no significant difference among the groups for mean age, female/male ratio, BMI, HAM-D scores, and the duration of illness. With respect to the mean YMRS scores, there was a significant difference among the groups.

The mean cholesterol levels were 139.2 ± 13.4 mg/dl in patients with manic episodes, 148.6 ± 14.8 mg/dl in patients with bipolar I disorder in full remission and 191.3 ± 16.1 mg/dl in controls. A significant difference in mean serum cholesterol among the groups was found, with BMI and age as covariates ($F = 3.67$, $p < 0.01$ adjusted for BMI; $F = 4.12$, $p < 0.05$ adjusted for age). When comparing the mean cholesterol level between the sexes within each group, no statistically significant difference was found ($p > 0.05$ for all groups).

The leptin levels were decreased in 9 (56.3%) patients with manic episodes, in 7 (43.8%) patients with bipolar I disorder in full remission and in 1 (6.3%) control, when individually compared with normal leptin levels adjusted for BMI and gender. The mean leptin levels were 4.4 ± 2.9 ng/ml in patients with manic episodes, 7.7 ± 4.5 ng/ml in patients with bipolar I disorder in full remission and 16.8 ± 6.4 ng/ml in controls. A significant difference in mean leptin levels among the groups was found, with BMI and age as covariates ($F = 3.36$, $p < 0.05$ adjusted for BMI; $F = 3.06$, $p < 0.05$ adjusted for age). When comparing the mean leptin level between the sexes within each group, it was significantly higher in females than in males with manic episodes ($p < 0.05$), but not in those with bipolar I disorder in full remission nor in controls ($p > 0.05$).

There was a positive correlation between cholesterol and leptin levels in all groups ($r = 0.63$, $p < 0.05$ for patients with manic episodes; $r = 0.58$, $p < 0.05$ for patients with bipolar I disorder in full remission and $r = 0.53$, $p < 0.05$ for the control group). There were positive correlations between cholesterol levels and BMI for patients with manic episodes ($r = 0.71$, $p < 0.05$) and for patients with bipolar I disorder in full remission ($r = 0.60$, $p < 0.05$), and between leptin levels and BMI in all groups

Table 1. General characteristics, scale scores, and leptin and cholesterol levels in the patients and controls

	Group I (patients with manic episodes, n = 16)	Group II (patients with bipolar I disorder in full remission, n = 16)	Group III (controls, n = 16)	p value
Age, years	27.8±8.2	28.2±7.8	28.4±6.9	>0.05
Sex, F/M	9/7	8/8	8/8	>0.05
Duration of illness, years	4.2±2.9	4.4±3.1	–	>0.05
BMI	24.4±2.4	23.9±3.1	24.0±3.4	>0.05
YMRS	30.2±4.8	5.7±2.4	5.2±2.1	<0.001 I-II, I-III
HAM-D	5.4±2.4	6.2±3.1	5.1±2.1	>0.05
Leptin, ng/ml	4.4±2.9	7.7±4.5	16.8±6.4	<0.01 I-II <0.001 I-III, II-III
Total cholesterol, mg/dl	139.2±13.4	148.6±14.8	191.3±16.1	<0.05 I-II <0.001 I-III, II-III

Results are means ± SD.

(r = 0.63, $p < 0.05$ for patients with manic episodes; r = 0.58, $p < 0.05$ for patients with bipolar I disorder in full remission and r = 0.53, $p < 0.05$ for the control group). No correlation was found between cholesterol levels and age or HAM-D scores for all groups. Likewise, no relation was found between leptin levels and age, or HAM-D scores for all groups. Leptin levels were correlated with the length of illness not only for patients with manic episodes (r = 0.65, $p < 0.05$) but also for patients with bipolar I disorder in full remission (r = 0.56, $p < 0.05$). On the other hand, cholesterol levels were correlated with the length of illness only for patients with manic episodes (r = 0.65, $p < 0.05$). In patients with manic episodes, there were negative correlations between YMRS scores and serum cholesterol (r = 0.65, $p < 0.05$) or leptin levels (r = 0.69, $p > 0.05$).

Discussion

The major findings of our study are as follows: (1) both patients with manic episodes and those with bipolar I disorder in full remission had markedly low serum cholesterol and leptin levels compared with controls, although the difference was more obvious in patients with manic episodes; (2) there were negative correlations between YMRS scores and serum cholesterol or leptin levels in the patients with manic episodes, and (3) there was a positive correlation between mean cholesterol and leptin levels.

Low cholesterol levels have been found in patients with manic episodes [6, 26]. This is also supported by this study. It has been reported that low cholesterol levels in manic episodes may be associated with increased physical activity and dietary changes and that it is important to verify whether recovered manics tend to maintain low cholesterol levels [6]. In these circumstances, in the present study, the finding that the patients with bipolar disorder in full remission also had low serum cholesterol levels compared with controls is an important finding. To the best of our knowledge, this is the first study on leptin levels in patients with bipolar disorder. The conditions regulated by leptin, e.g. food intake [18], sexual behavior [19] and locomotion [20], and sleep-wake regulation which interacts with leptin [21] are considerably affected in manic episodes. In our study, both patients with manic episodes and those with bipolar I disorder in full remission had low leptin levels compared with controls, although the difference was more obvious in patients with manic episodes. These findings might suggest that both serum cholesterol and leptin are associated not only with manic episodes but also with recovered periods of the illness. A positive correlation between serum leptin concentration and total cholesterol has been reported [15] and is supported by this study. An interaction between leptinergic and serotonergic systems in the central nervous system has been shown [16] and it was noted that leptin administration stimulated serotonin turnover [27]. On the other hand, diminished serotonergic neurotransmission has been implicated in manic episodes. Serotonin modulates different neuronal activities in the central nervous system and, as a result, many physiological and behavioral func-

tions, i.e. sleep, appetite, and impulse control and low serotonin activity are discussed to be the reason for many behavioral abnormalities like suicide attempts, agressivity, and disturbed sleep; some of them frequently occur in bipolar patients [17]. It has been suggested that reduced plasma cholesterol could suppress the cholesterol/phospholipid ratio in neuronal membranes with consequent alterations in membrane fluidity, viscosity and function, including serotonin (5-HT) receptors and serotonergic neurotransmission [28]. Therefore, these relationships allowed us to consider that leptin might be associated with manic episodes and bipolar I disorder in full remission. The exact roles of cholesterol, leptin and serotonin which seem to be related with each other have been obscured due to the dearth of investigations.

Several limitations should be taken into consideration when interpreting our results. First, the relatively small sample size might not be representative of patients with bipolar disorder in manic state or full remission. Apart from this, we could not control the economic status and other psychosocial factors which might be related to serum total cholesterol or leptin. In conclusion, the patients with manic episodes and those with bipolar I disorder in full remission seem to be associated with decreased serum cholesterol and leptin levels. However, this is obviously only a suggestion and needs to be confirmed by more comprehensive studies dealing with leptin, cholesterol and indices of serotonin altogether.

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