Alterations of Lipid-Lipoprotein and Leptin in Bipolar Disorder Associated with Clinic Process

Bipolar Bozuklukta Klinik Süreç ile İlişkili Lipit-Lipoprotein ve Leptin Değişimleri

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ABSTRACT

Introduction: Obesity is more common among patients with bipolar disorder as compared to normal population. There are studies showing increased leptin levels in obese patients. The aim of the present study was to investigate the alterations in leptin levels, body mass index (BMI), and lipid-lipoprotein levels during manic period, as well as during euthymic period, after one month in patients with bipolar disorder.

Methods: Thirty-one adult patients, who had been hospitalized in the psychiatry clinic because of manic period of bipolar disorder, were included in the present study. Serum leptin and lipid-lipoprotein levels and BMI of the patients were analyzed both on the first day and 30th day of hospitalization after they became euthymic.

Results: Total cholesterol and triglyceride levels significantly increased in male patients ($p<.05$). The increase in total cholesterol and LDL-C levels was not significant in female patients ($p=.066$ and $p=.056$, respectively). BMI was significantly, but slightly increased in both genders ($.56\pm.14$ kg/m²), however, such a change was not observed in serum leptin levels.

Conclusion: Results of the present study demonstrated that clinical improvement in bipolar patients showed different association in each gender with the alterations in BMI and serum lipid and/or lipoprotein levels. Such an alteration might have resulted from direct or indirect effect of drugs, as well as from lifestyle changes. (*Archives of Neuropsychiatry 2014; 51: 52-56*)

Key words: Bipolar disorder, leptin, lipid-lipoprotein, body mass index

Conflict of interest: The authors reported no conflict of interest related to this article..

ÖZET

Amaç: Bipolar bozukluk hastalarında obezitenin normal topluma göre daha sık görüldüğü saptanmıştır. Obez hastalarda leptin düzeylerinde artış olduğunu saptayan çalışmalar mevcuttur. Bu çalışmada bipolar bozuklukta manik dönem ve bir ay sonraki ötimi döneminde leptin, vücut kitle indeksi, lipit-lipoprotein değişimleri incelemeyi amaçlanmıştır.

Yöntem: Çalışmaya psikiyatri servisine Bipolar bozukluk manik dönem tanısı ile yatırılan 31 erişkin hasta alınmıştır. Hastaların yatıtlıkları birinci gün ve ötimi sağlandıktan 30 gün sonra serum leptin, lipit-lipoprotein ve vücut kitle indeksleri hesaplandı.

Bulgular: Erkek hastalarda total kolesterol ve trigliserit düzeyleri anlamlı bir artış göstermiştir ($p<.05$). Kadın hastalarda ise total kolesterol ve LDL-K artışları anlamlılık düzeyine ulaşmamıştır. Her iki cinste de vücut kitle indeksi anlamlı ancak küçük miktarda ($0,56\pm0,14$ kg/m²) artmış, ancak serum leptin düzeylerinde benzer bir değişim saptanmamıştır.

Sonuç: Sonuçlarımız bipolar hastalarında klinik iyileşmenin anlamlı vücut kitle indeksi ve serum lipit ve/veya lipoprotein değişimleri ile her iki cinste farklı özellik taşıyan ilişkisini göstermektedir. Bu değişim ilaçların doğrudan veya dolaylı etkisinden ve yaşam tarzı değişikliklerinden kaynaklanabilir. (*Archives of Neuropsychiatry 2014; 51: 52-56*)

Anahtar kelimeler: Bipolar bozukluk, leptin, lipit-lipoprotein, vücut kitle indeksi

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Bipolar disorder is a chronic disorder characterized with manic and depressive periods where the patient can become completely euthymic between these periods (1). Patients with bipolar disorder carry a higher risk in terms of obesity, metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension and cardiovascular disease compared to the normal population. The risk factors for increased weight and dyslipidemia in patients

with bipolar disorder include comorbid excessive eating disorder, depressive periods, excessive consumption of carbohydrates and lack of exercise (2). The drugs used for treatment of bipolar disorder also may lead to weight gain (3).

Leptin is a hormone which is mainly secreted from white and brown adipose tissue cells regulating food intake and energy consumption by transferring information to the hypothalamus about the amount of fat in the body (4,5). High serum levels are frequently related with leptin resistance and obesity (6,7). It is

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known that the effects of leptin on the mood are mediated by corticotropin releasing hormone and neuropeptide Y (8,9,10). Neuropeptide Y in the hypothalamus is a significant molecule which stimulates appetite (11,12). Leptin suppresses the level of neuropeptide Y (11,12).

It has been proposed that plasma lipid levels also have effects on the mood. It has been proposed that treatment approaches directed to lower cholesterol increase the risk of impulsive-aggressive behavior and mortality related with suicide. Low cholesterol levels have been found to be associated with different psychiatric diseases including depression, attention deficit and antisocial personality disorder. It has been reported that leptin reduces intracellular lipid concentration by reducing synthesis of fatty acids and triglyceride and increasing fat oxidation (13).

In this prospective study, we measured the levels of leptin, triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) and BMI values in the manic period and during the euthymic period provided after a 30-day treatment period in a group of patients with bipolar disorder. We aimed to evaluate if there was a relation between the lipid panel and leptin levels in the manic and euthymic periods in patients with bipolar disorder.

Methods

Thirty-one adult patients who presented to Gaziantep University, Medical faculty, Department of Psychiatry Mood Disorders Unit for the objective of treatment, who were diagnosed with bipolar disorder according to the DSM-IV diagnostic criteria and who were hospitalized while having a manic attack were included in our study. The diagnoses were made by at least one specialist physician. Local ethics committee approval was obtained from Gaziantep University Medical Faculty ethics committee. Informed consent was obtained from the patients and their relatives. The patients with alcohol addiction or abuse, a history of use of cholesterol lowering drugs, chronic disease, mental retardation and additional psychiatric disease were excluded from the study. Drug selection in patients in whom typical or atypical antipsychotic and antimanic drugs were initiated for clinical treatment was determined naturalistically independent of the study.

The Bech-Rafaelsen Mania Scale, Clinical Global Impression and Hamilton Depression Scale scores of 31 patients included in the study were recorded on the first day at presentation (at the time of manic attack) and on the 30th day. Body weight and body mass index measurements were done on the first day and on the 30th day. A routine hospital diet ranging between 1800 and 2000 calories was given to the patients. This routine hospital diet included 40-45 g protein, 300-400 g carbohydrate and 50-55 g fat. Before treatment blood samples were obtained from the patients at 08:00-10:00 after 12-14 hour fasting for routine tests and a 5 mL venous blood sample was placed in a plain tube

and serum samples were kept in deep freeze at -20°C for analysis of lipid, lipoprotein and leptin until the date of studying. The lipid, lipoprotein and leptin levels were measured in Gaziantep University, Medical Faculty, Department of Biochemistry. Body mass index was obtained by dividing body weight in kg to the square of height in m.

Serum leptin levels were measured by enzyme linked immunosorbent assay (ELISA) method. Bio source-International commercial leptin kit was used for the measurements (Human leptin ELISA, BioSource International, California, USA).

Statistical analysis

SPSS 10.0 (SPSS Inc.) statistical program was used for analysis of the data. The results were presented as mean $\pm$ standard error or median (Min.-Max.) values. In assessment of the data belonging to the first day and 30th day in the manic period, the significance test with dependent samples was used for comparison of the data which showed a normal distribution and Wilcoxon Rank test was used for comparison of the data which did not show a normal distribution. The contribution of various factors to the alternation in the leptin levels before and after treatment in all patients was investigated with generalized linear model. A p value of <.05 was considered significant in all statistical assessments.

Results

Sixteen of the patients were female and 15 were male. The mean age was 32.6 ± 2.8 years in women and 31.9 ± 2.1 years in men. Twenty-one of the patients had not received treatment before, discontinued treatment or had received electroconvulsive treatment at the time of presentation. Four patients were receiving atypical antipsychotic (3 quetiapine, 1 olanzapine), one patient was receiving mood stabilizer (carbamazepine), five patients were receiving mood stabilizer plus atypical antipsychotic (2 olanzapine, 2 risperidone, 1 quetiapine in combination with lithium). During the one-month treatment period, seven of the patients were treated with atypical antipsychotics (4 olanzapine, 2 quetiapine, 1 risperidone), five were treated with typical antipsychotics (3 haloperidol, 2 zuclopentixol), one was treated with mood stabilizer (oxcarbamazepine), twelve were treated with atypical antipsychotic plus mood stabilizer (2 valproic acid 10 lithium in combination with 6 quetiapine, 4 olanzapine, 2 risperidone), six were treated with mood stabilizer plus typical antipsychotic (2 valproic acid and 4 lithium in combination with 4 chlorpromazine, 1 neurodol, 1 pimozide). The Bech-Rafaelsen Mania Scale, Clinical Global Impression and Hamilton Depression Scale scores of 31 patients included in the study measured on the first day and 30th day are shown in Table 1.

The lipid levels found in both genders in the manic and euthymic periods were grouped according to the USA National Cholesterol Education Program Adult Treatment Panel III.

The lipid, lipoprotein metabolism and leptin levels and the differences observed after treatment were evaluated independently

in male and female patients, because these parameters show significant differences by gender. A significant increase was found in total cholesterol and triglyceride levels in male patients after treatment ($p=.05$ and $p=.038$, respectively). The HDL-C and LDL-C levels did not show significant difference ($p>.05$).

The total cholesterol, triglyceride, HDL-C, VLDL-C and LDL-C levels measured on the first day and 30th day in male patients are shown in Table 2.

The total cholesterol, triglyceride, HDL-C, VLDL-C and LDL-C levels measured on the first day and 30th day in female patients are shown in Table 3. A significant increase was observed in female patients in total cholesterol and LDL-C levels, but these alterations did not reach the statistically significance level ($p=.066$ and $p=.056$, respectively). The triglyceride and HDL-C levels did not show alternation ($p>.05$).

When the lipid levels of both genders in the manic and euthymic periods were examined it was found that the number of fe-

male patients with a cholesterol level above 200 mg/dL increased from three in the manic period to six in the euthymic period (18.8%/37.5%) and the number of male patients with a cholesterol level above 200 mg/dL increased from two in the manic period to six in the euthymic period (13.3%/40%). The number of patients with baseline triglyceride level above 150 mg/dL was found to be four in women and two in men. After treatment, these figures changed to three and seven, respectively (F: 25%/18.8 and M 13.3%/46.7%). The number of patients with a HDL-C level below 40 mg/dL did not change in the male patients (46.7%) and increased from seven to eight in female patients (43.8%/50%). The number of patients with a LDL-C level above 100 mg/dL increased from nine to twelve in female patients (56.3%/75%) and from seven to ten in male patients (46.7%/66.7%).

29% of the patients in our study group were found to be overweight (Body mass index: 25-29.9 kg/m², $n=9$; 6 female and 3 male patients) and 12.9% were found to be obese (Body mass index >30 kg/m², $n=4$; 4 female patients). It was found that 6.5% of the patients were lean (Body mass index <20 kg/m², $n=2$, 2 male patients). In the subgroups divided by gender, the frequency of obesity was found to be 25% in the female patients. The frequency of overweight was found to be 37.5% in the female patients and 20% in the male patients. The mean weight gain in the patients in our study group was found to be $.56 \pm .14$ (mean $\pm$ standard error, min.-max.: 0-2 kg). A significant increase in BMI was found in the male patients after treatment, whereas no change was observed in systemic leptin levels ($p=.013$ and $p>.05$, respectively). A significant increase in BMI was found in the female patients after treatment, whereas no change was observed in systemic leptin levels ($p=.028$ and $p>.05$, respectively). The BMI values and leptin levels in the male and female patients on the first day and 30th day are shown in Table 4.

Discussion

The frequency of overweight and obesity were found to be 29% and 12.9%, respectively, in the patients in our study group. In addition, it was observed that 6.5% of the patients were lean. When the study group was divided into subgroups by gender, the frequency of obesity was found to be 25% and the frequency of overweight was found to be 37.5% in the female patients. Obesity was not found and the frequency of overweight was found to be 20% in the male patients. Different values related with obesity prevalence have been reported in patients with bipolar disorder. Fagiolini et al. (14) reported the frequency of obesity to be 45% and the frequency of overweight to be 29%

Table 1. BRS, HDS and CGI scores in the manic period and euthymic period in patients with BPD

	First day	30 th day	Significance
BRS	25.2 $\pm$ 1.6	6.6 $\pm$ 1.4	.000
CGI	5.8 $\pm$.2	1.35 $\pm$.79	.001
HDS	2.8 $\pm$.5	1.4 $\pm$.3	.648

Table 2. Total cholesterol, triglyceride, HDL-C, VLDL-C and LDL-C levels on the first day and 30th day in the male patients

	First day	30 th day	p
Total cholesterol (mg/dL)	165.6 $\pm$ 8.1	186.8 $\pm$ 12.4	.05
Triglyceride (mg/dL)	111.0 $\pm$ 17.7	152.4 $\pm$ 18.2	.038
HDL-C (mg/dL)	40.8 $\pm$ 3.4	39.0 $\pm$ 4.0	.691
LDL-C (mg/dL)	102.5 $\pm$ 6.7	117.4 $\pm$ 10.8	.156

Table 3. Total cholesterol, triglyceride, HDL-C, VLDL-C and LDL-C levels on the first day and 30th day in the female patients

	First day	30 th day	p
Total cholesterol (mg/dL)	177.6 $\pm$ 11.0	193.0 $\pm$ 11.0	.066
Triglyceride (mg/dL)	115.1 $\pm$ 10.8	117.8 $\pm$ 16.0	.623
HDL-C (mg/dL)	43.0 $\pm$ 4.4	42.4 $\pm$ 5.0	.679
LDL-C (mg/dL)	112.0 $\pm$ 11.0	127.1 $\pm$ 8.7	.056

Table 4. BMI and leptin values on the first day and 30th day in the female and male patients

	First day	Female 30 th day	Significance	First day	Male 30 th day	Significance
BMI (kg/m ²)	24.3	24.5	.02	23.4	26.5	.01
Leptin (ng/mL)	8.6	8.3	.06	2.0	2.7	.46

in 171 patients with bipolar disorder. McElroy et al. (15) reported the frequency of obesity to be 21%, the frequency of overweight to be 31% and the frequency of morbid obesity to be 5% in 644 patients with bipolar disorder. In the study of Elmslie et al. conducted in New Zealand in 89 patients with euthymic bipolar disorder, the frequency of overweight was reported to be 44 and the frequency of obesity was reported to be 20% in women. They found that the frequency of overweight (29%) was not different, but the frequency of obesity (19%) was higher compared to the healthy population in male patients (16). In our study, the results were found to be similar to previous studies when the groups were evaluated by gender. In contrast, the frequency of obesity was found to be lower compared to previous studies when gender discrimination was not made.

When our results were evaluated together with the studies conducted with the Turkish population, they were not found to support the general assumption that the frequencies of overweight and obesity in the manic period in patients with bipolar disorder are higher compared to the healthy population. In the prevalence study conducted in Turkey, the prevalence of obesity was found to be 35% (17). In another field study, obesity was found with a rate of 25.3% in men and with a rate of 44.2% in women (18). In the study of Gergeroğlu et al. conducted in Gaziantep region including 61 patients with bipolar disorder, BMI was found to be 24.14 in the patient group and 24.05 in the control group (19).

Another significant finding of our study was that there was a significant increase in BMI measurements after one month compared to the time of admission. However, there was no change in systemic leptin levels in parallel to this finding. Increase in BMI is expected to lead to an increase in systemic leptin levels. This change occurs in proportion with weight gain under normal conditions. Our study did not support this data.

McIntyre et al. (20) showed that weight gain induced by antipsychotics in patients with bipolar disorder was related with plasma leptin levels. However, they reported that the changes in leptin levels in the circulation gained significance only in the 4th month. McIntyre et al. (20) showed that a weight gain of 13% increased leptin levels by 56% by the 6th month of treatment. In patients with a predisposition to suicide and in patients who had attempted suicide, BMI values were not found to be different compared to healthy controls, but leptin levels were found to be significantly lower (13). Similarly, BMI was not found to be different in patients with bipolar disorder I compared to the control group, whereas leptin levels were found to be significantly lower (21). Gergerlioğlu et al. did not find BMI and systemic leptin levels to be different in patients with euthymic bipolar disorder compared to the control group. Atmaca et al. found that the leptin levels increased significantly together with BMI in 15 hospitalized patients with bipolar disorder after a 8-week lithium treatment period. In this study, weight gain was more prominent and all patients received lithium monotherapy (22).

In our study, lipid and lipoprotein alterations after treatment were evaluated in patients with bipolar disorder and it was found that total cholesterol and triglyceride levels increased in

the male patients and statistically insignificant increases were observed in total cholesterol and LDL-C levels in the female patients. When we compared our study group with the prevalence study conducted in Turkey, we found that the prevalence of hypercholesterolemia in patients with bipolar disorder was lower in the manic period and higher on the 30th day compared to the general population. The prevalences of abnormalities in LDL-C and HDL-C levels were higher and the prevalence of hypertriglyceridemia was lower compared to the general population.

Atmaca et al. (21) found serum total cholesterol levels to be lower in patients with bipolar disorder in remission and in the manic period compared to healthy controls. They proposed that low cholesterol levels in the manic period might be related with changes in physical activity and feeding habits (21). Ghaemi et al. (23) found the total cholesterol level to be lower in manic patients compared to the depressive and complex periods.

The limitations of our study included the fact that the treatment period was not long enough to observe the changes in leptin levels, lack of classification by drugs and lack of a control group. Our study is a preliminary study because of these limitations. Longer follow-up studies and studies including classification by drug groups will provide more detailed information in the future.

In conclusion, our study showed that clinical improvement provided by a one-month treatment period in patients with bipolar disorder who were in the manic period caused to an increase in BMI in both genders, but this small change was not reflected in serum leptin levels. In this process, total cholesterol and triglyceride levels increased in the male patients and a statistically insignificant increase in total cholesterol and LDL-C levels was observed in the female patients.

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