Correlation Between Metabolic Syndrome and Serum Ghrelin Levels in Bipolar Patients

**ABSTRACT**

**Objective:** The aim of this study is to investigate whether serum ghrelin levels are associated with metabolic syndrome (MetS) in bipolar patients.

**Methods:** A total of 60 bipolar disorder patients and 30 healthy volunteers were included in the study. The patient group was separated into two subgroups according to the use of atypical antipsychotics (AA)-risperidone, quetiapine, olanzapine or mood stabilizers (MS)-lithium, valproic acid, carbamazepine, lamotrigine. The serum ghrelin level was measured by human ghrelin ELISA kits. Patients were diagnosed with MetS according to the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP ATP 3) criteria; MetS was considered present when 3 or more criteria were met.

**Results:** Among bipolar patients included in the study, 51.7% (n=31) were treated only with AA, while 48.8% (n=29) were treated with MS alone. MetS diagnosis was established in 36.7% (n=22) of patients. There was no significant difference in ghrelin levels when comparing patients with and without MetS. Additionally, there were no significant differences among the patients with MetS using AAs and among the patients with MetS using MSs in terms of ghrelin levels. The serum ghrelin levels were found to be significantly lower in bipolar patients compared to controls. Negative correlation was detected between ghrelin and fasting blood glucose.

**Conclusion:** Our study found that, compared to the general population, MetS was more frequently observed in bipolar patients and that serum ghrelin level was significantly lower in those patients. This result might be associated either with a compensatory mechanism or with an involvement of other disease-specific parameters. (Archives of Neuropsychiatry 2010; 47: 328-32)

**Key words:** Bipolar disorder, metabolic syndrome, ghrelin

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**ÖZET**

Amaç: Bu araştırmada ikiuçlu bozukluk hastalarında serum ghrelin düzeyleri ve Metabolik Sendrom (MetS) arasındaki iliskinin olup olmadığını incelemesini amaçlanmıştır.


Bulgular: Çalışmaya alınan bipolar hastalarının %51.7’si (n=31) sadece atipik antipsikotik (AA) tedavisi alırken, %48.8’ü (n=29) sadece duygu düzenleyici (DD) kullanıyordu. Hasta grubunda %36.7 (n=22) hastaya MetS tanısı konulmuştur. Hasta grubunda MetS olan ve olmayanlar arasındaki ghrelin düzeyleri açısından anlamlı fark yoktu. İlaçtan AA kullanılan ve MetS gelişen hastalarda ghrelin düzeyleri açısından anlamli farklı yoktu. DD kullanılar ve Mets geliştirmiş olan hastalarda ghrelin düzeylerinin açısından anlamli fark yoktu. Serum ghrelin seviyeleri kontrol grubu ile kıyaslandığında bipolar hastalarda anlamlı oranda düşük bulunmuştur.


Anahtar kelimeler: Ikiuçlu bozukluk, metabolik sendrom, ghrelin
Introduction

Ghrelin is a peptide hormone that binds to growth hormone (GH) receptors and is primarily secreted by the acidophil cells in the gastric fundic mucosa. The central nervous system (CNS), heart, muscle tissue, adipose tissue, endocrine glands (i.e. pancreas, thyroid) and the gastrointestinal system have been shown to also secrete this hormone (1,2). Ghrelin is related with eating and weight gain. Its secretion has been found to increase before meals and decrease after meals (3).

Ghrelin was initially discovered as a result of its GH-releasing properties (4). Studies have demonstrated that ghrelin infusion increases circulating plasma GH in both rodents and humans (5-9), and has been recently identified as the endogenous ligand of the GH secretagogue receptor (GHS-R). Ghrelin is produced by the P/D1 cells, a cell-type distinct from the other enteroendocrine cells. These cells also express the vascular monoamine transporter type 2 (VMAT-2), suggesting a role of monoaminergic transmission in the regulation of ghrelin secretion (2).

Another crucial property of ghrelin is its orexigenic effect. It acts by stimulating agouti gene-related protein (AGRP), neuropeptide Y (NPY), orexin A and B. Ghrelin also counteracts the anorectic effect of leptin in the CNS and has effects on glucose metabolism and insulin release (10,11), gastric acid secretion and motility (12), fasting and fed motility (13), cardiovascular actions (14,15), and food intake and control of energy balance (16,17).

Higher incidence of significant weight gain, high blood glucose and triglyceride (TG) levels has been reported with second-generation antipsychotic (SGA) treatment, as the number of treated patients and available follow-up data have increased. The higher risk for cardiovascular disease leading to morbidity and mortality can be explained by the obesigenic and diabetogenic properties of these drugs. If the weight gain is substantial, it can lead to a reduced quality of life and treatment adherence, with a higher incidence of relapse. It is possible that antipsychotic treatment leads to weight gain and alteration of carbohydrate metabolism through increased appetite. These drugs have a high affinity to various monoaminergic receptors, such as serotonin receptors 5-HT2A and 2C or histamine receptor H1. These receptors also have a role in modifying food intake. The strongest correlation between body weight gain and receptor affinity has been reported for H1 receptor (18,19).

Atypical antipsychotics (AA) provide an important treatment option for bipolar patients who are manic and/or psychotic. However, over the recent years, there has been growing concern about the potential metabolic side effects of antipsychotics. Physical changes such as weight gain may be an indication of metabolic side effects in patients treated with AA (20,21). These drugs may cause obesity and other components of metabolic syndrome (MetS).

Physical disorders such as obesity, hyperlipidemias, hypertension, and type 2 diabetes mellitus are becoming recognized as significant comorbidities in patients with bipolar disorder (BD) (22-30).

MetS affects many organ systems. Among several psychiatric disorders, MetS has mostly been studied in schizophrenia patients (31-33), although there are recent investigations in BD patients as well (34,35). Yumru et al. found that MetS prevalence in BD patients was 32%. They also observed a significant correlation between MetS and AA use (36).

Recently, the relationship between ghrelin levels, several psychiatric disorders, and particularly AA drug use has been the focus of interest in a number of articles published in the literature (37-40). These studies offer generally consistent evidence that AA treatment is associated with an increased risk of metabolic side effects. Changes in serum ghrelin levels may lead to metabolic side effect in bipolar patients. To our knowledge, there have been no prior studies investigating the possible relationship between MetS and serum ghrelin levels in BD patients. The aim of this study was to investigate whether there is an association between serum ghrelin levels and MetS in BD patients.

Methods

Subjects
A total of 60 euthymic BD patients, admitted to the Gaziantep University School of Medicine, Department of Psychiatry, Mood Disorders Unit, using either mood stabilizers (MS) or AA for at least 3 months prior to the study and 30 healthy volunteers were included in the study. Each patient was assessed and diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (41). All patients were evaluated through a semi-structured interview. Those with comorbid psychiatric disorders were excluded. Other exclusion criteria were comorbid systemic diseases such as hypertension, diabetes mellitus or endocrinopathy, history of alcohol or other substance abuse and dependency, and use of cholesterol-lowering medications. The patient group was separated into two subgroups according to the use of AA (risperidone, quetiapine, olanzapine) or MS (lithium, valproic acid, carbamazepine, lamotrigine). Patients taking any additional psychotropic drugs other than these were also excluded.

The control group consisted of 30 individuals with a similar body mass index (BMI), sex, and age to the patient group, and no past or present history of any psychiatric disorder. None of the control group patients were using any psychotropic or cholesterol-lowering drugs. Written informed consent was obtained from all participants and approval from the Ethics Board of Gaziantep University, School of Medicine was granted.

Biochemical Analyses
Venous blood samples were collected from the antecubital vein after a 12-hour fasting period. Standard empty test tubes were used for the measurement of ghrelin, glucose, high-density lipoprotein (HDL) and TG levels. Serum lipid levels were measured using enzymatic calorimetric method (Roche-Hitachi Modular Analytics, Tokyo, Japan) in a biochemical autoanalyser. Serum ghrelin levels were determined with human ghrelin ELISA kits at the Biochemistry Laboratory of Selcuk University, School of Medicine.

Blood pressure was measured following a 5-minute rest in the sitting position. Waist circumference was measured at the umbilical level. MetS diagnosis was established in the presence of 3 or more criteria according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines (42):

1. Abdominal obesity: waist circumference above 102 cm in women and 88 cm in men;
2. High TG: level above or equal to 150 mg/dL (1.69 mmol/L);
3. Low HDL cholesterol: level below 50 mg/dL (1.29 mmol/L) in women and 40 mg/dL (1.04 mmol/L) in men;
4. High blood pressure: level above or equal to 130/85 mmHg.
5. High fasting blood glucose: level above or equal to 110 mg/dL (≥6.1 mmol/L).

Statistical Analysis
The software Statistical Package for the Social Sciences (SPSS) version 10.0 was used for statistical analysis. Mann-Whitney U test was applied for the comparison between patient groups and controls as well as between ghrelin and other biochemical parameters. Chi-square test and Fisher’s exact test were used to compare sex distribution both in the patient and control groups as well the presence of MetS according to gender and drug use. Spearman’s rank correlation test was used for the correlation analysis of nonparametric variables. A p<0.05 was considered as statistically significant.

Results
The mean age of 60 bipolar patients was 34.38±11.05 years, the mean disease duration was 118.5 months, and the mean BMI was 27.33±5.30 kg/m². Married patients represented 63.3% of the group, followed by single patients with 33.3% (n=20) and divorced with 3.3% (n=2). Mean education duration was 8.4±3.6 years and employment rate was 41.7% (n=25).

AA treatment was received by 51.7% (n=31) of patients and BS treatment-by the remaining 48.8% (n=29).

Of the patients using AA, 32.3% (n=10) were on risperidone (mean dose=4.5±1.0 mg/day), 32.3% (n=10)-on olanzapine (mean dose=13.0±8.2 mg/day), and 35.5% (n=11)-on quetiapine (mean dose=600.0±354.9 mg/day). Of the patients taking MS, 72.4% (n=21) were on lithium (mean dose=1186.0±172.6 mg/day), 13.8% (n=4)-on valproic acid (mean dose=1600.0±223.6 mg/day), 6.9% (n=2)-on lamotrigine (mean dose=150.0±70.7 mg/day), 3.4% (n=1)-on carbamazepine (dose=800 mg/day), and 3.4% (n=1) were on a combination of lithium and valproic acid.

MetS diagnosis was established in 36.7% (n=22) of patients. The percentage distribution of MetS diagnostic criteria is presented in Table 2. There was no sex-related difference between patients with or without MetS (χ²=0.60; df=1; p=0.28). When assessing whether there was a difference between AA and MS patients with respect to having MetS, it was found that more patients in the AA group were diagnosed with MetS (χ²=8.86; df=1; p=0.003) (Table 1).

No significant differences were found between the three AA drugs (risperidone, quetiapine, olanzapine) in terms of MetS prevalence (χ²=0.86; df=2; p=0.05). Similarly, no significant differences were found between the four MS drugs (lithium, valproic acid, carbamazepine, lamotrigine) in terms of MetS prevalence (χ²=0.18; df=2; p=0.05). MetS was significantly more frequent in unemployed patients (χ²=0.86; p=0.007).

No significant differences were found between the AA group patients (Z= -2.2; p>0.05) and between the MS group patients (Z= -2.1; p>0.05) in terms of ghrelin levels. There was no significant difference between those patients with or without MetS regarding ghrelin levels (Z= -1.2; p>0.05). There was no significant difference in terms of ghrelin levels within the patient diagnosed with MetS and using AA (Z= -0.59; p>0.05) and within the patients diagnosed with MetS and using MS (Z= -0.59; p>0.05). There was no significant difference between the genders with respect to ghrelin levels (Z= -1.58; p>0.05). Ghrelin levels were significantly lower in bipolar patients compared to controls (Z= -2.5; p=0.01). Ghrelin levels were significantly lower in patients with high blood glucose, and a negative correlation was detected (R= -0.31; p=0.01). No significant correlation was found between ghrelin levels and other MetS sub-parameters such as blood pressure, obesity, HDL, TG, and abdominal obesity (Table 2).

Discussion
Our study was the first investigating the correlation between serum ghrelin levels and MetS in BD patients.

The studies concerning BD and MetS were limited in the literature. The prevalence of MetS in BD patients has been reported as 30% in a recent study (35). Yumru et al., who described a relationship between MetS and AA use in bipolar patients, reported a MetS prevalence of 32% (36). The prevalence of MetS in the general Turkish population has been reported as 17.9% (43).

Similarly to previous investigations, the MetS prevalence in our study was 36.7% in the patient group. Recently, there have been records of high MetS prevalence in patients using AA (20, 34, 36). In agreement with the results of Yumru et al., it was found that MetS was more frequent in patients using AA when compared to those using MS. Furthermore, there were no significant differences between the AA sub-types in terms of MetS prevalence. The fact that MetS was significantly more common in unemployed patients is noteworthy, since it demonstrates the negative effects of a sedentary lifestyle on metabolic parameters.

Lack of measurement of metabolic parameters in the control group limited our evaluation throughout the study since we could not assess the relationship between ghrelin levels and metabolic parameters in controls and further compare it with the patients. Nevertheless, we were able to perform a comparison between bipolar patients and controls regarding serum ghrelin levels and to determine the correlation between ghrelin levels and metabolic parameters in the patient group.

Palik et al., when comparing ghrelin levels between a heterogeneous patient group using AA and controls, found that

| Table 1. Distribution of MetS diagnostic criteria |
|-----------------|----------|---|
| High blood pressure | 14 | 23.3 | Z= -0.6; p=0.6 |
| Abdominal obesity | 29 | 48.3 | Z= -2.4; p=0.06 |
| High fasting blood glucose | 7 | 11.7 | Z= -2.5; p=0.001* |
| Low HDL cholesterol | 26 | 43.3 | Z= -1.1; p=0.9 |
| High triglycerides | 33 | 55.0 | Z= -1.6; p=0.2 |
| MetS | 22 | 36.7 |

| Table 2. Metabolic syndrome percents according to drug types |
|-----------------|----------|---|
| AA (N=31) | MS (N=29) | Analysis |
| Patient with the MetS | 16 (%51) | 6 (%21) | p=0.003 |
| Patients without the MetS | 15 (%49) | 23 (%79) | p=0.003 |
ghrelin levels were higher in patients using AA, and suggested that AA could increase ghrelin (40). No significant difference in ghrelin levels between patients and controls was found in our study. This might be due to two reasons. Firstly, our sample represented a more specific patient group, possibly affected by different biological parameters. Secondly, an initial deterioration in metabolic parameters via ghrelin-acting pathways might have occurred, leading to the higher MetS frequency, particularly in patients using AA; however, in time, a compensatory mechanism could have led to a rebound reduction in ghrelin levels.

It has been reported that ghrelin is negatively correlated with postprandial blood glucose, BMI, and serum TG levels in patients using AA (40). In our study, except for fasting blood glucose, no correlation was found between ghrelin levels and MetS parameters. Our patient population consisted not only of AA users, but also of MS users. Nevertheless, no significant difference could be detected between MS and AA patients in terms of ghrelin levels.

Alternatively, the negative correlation between ghrelin and fasting blood glucose in bipolar patients supports the hypothesis that ghrelin increases blood glucose by suppressing pancreatic insulin secretion in carbohydrate metabolism (44).

In conclusion, this study found that MetS was more frequent in BD patients compared to the general population, and that the presence of MetS was significantly associated with AA use. MetS prevalence was significantly higher in unemployed patients. Serum ghrelin levels were significantly lower in bipolar patients. This might be associated with either a compensatory mechanism or involvement of other disease-specific parameters. A negative correlation was observed between ghrelin and fasting blood glucose. No relationship between ghrelin and other metabolic parameters was found.

References