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The Prevalence of Metabolic Syndrome Parameters Among Bipolar Disorder Outpatients on Lithium Monotherapy

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ÖZET:

Lityum monoterapisi alan bipolar bozukluk hastalarında metabolik sendrom parametrelerinin yaygınlığı

Amaç: Bipolar bozuklukta atipik antipsikotik, duygudurum düzenleyicileri ya da kombine ilaç kullanımı ve geçirilmiş depresif dönemler metabolik sendromdan sorumlu tutulmaktadır. Lityum monoterapisinin kilo alımı ile ilişkili olduğunu bildiren yayınlar olmasına karşın, metabolik sendrom ile ilişkisini araştıran yayına rastlanmamıştır. Bu çalışmada, lityum monoterapisi alan, ötimik bipolar bozukluk hastalarında metabolik sendrom yaygınlığının araştırılması amaçlanmıştır.

Yöntem: Ötimik ve lityum monoterapisi altında olan hastaların Ocak 2009 ve Ocak 2011 tarihleri arasındaki dosya bilgileri taranmıştır. NCEP ATP III ölçütlerine göre metabolik sendrom parametreleri olan; trigliserid, yüksek dansiteli lipoprotein, açlık kan şekeri, bel çevresi ve tansiyon bileşenleri kaydedilmiştir. En az üç aydır lityum monoterapisi kullanan hasta dosyalarının verileri çalışmaya alındı. Son üç ay içinde lityum dışında başka psikotrop ilaç kullanmış, ardından lityum monoterapisine geçilmiş ya da beraberinde alkol madde kullanımı bildirilmiş hasta dosyaları çalışma dışında tutulmuştur.

Bulgular: Hastaların yaş ortalaması 40.47±11.41; kadınların yaş ortalaması 41.84±12.49 ve erkeklerin yaş ortalaması ise 38.88±9.61 (p=0.313) idi. İlk atak tipine bakıldığında hastaların 34'ü depresif, 29'u manik ve ikisinin karma atak yaşamış oldukları görüldü. Hastaların hastalık süreleri 16.70±9.86 ve tedavi süreleri 16.67±9.90 yıl idi. Hastaların kullandığı ortalama lityum dozu 1160±274 mg/gün ve ortalama kan düzeyleri 0.761±0.141 mEq/l idi. Lityum kullanma süresi 156.29±117.53 hafta idi. Hastaların ortalama BKİ 27.67±4.47 kg/m^2 ve bel çevresi 87.72±12.48 cm idi ve cinsiyetler arasında BKİ ve bel çevresi bakımından anlamlı bir fark yoktu (p=0.173 ve p=0.434, sırasıyla). Ortalama açlık kan şekeri düzeyi 87.86±15.53 mg/dl, total kolesterol düzeyi 180.29±47.38 mg/dl; HDL düzeyi 38.81±8.62 mg/dl; trigliserid düzeyi 136.57±108.08 mg/dl idi. Kesitsel olarak metabolik sendrom tanı ölçütünü karşılayan hasta sayısı on idi. Bu on hastanın dokuzu kadın, biri erkekti (χ^2=4.841, p=0.028).

Sonuç: Bipolar bozukluk olgularında, lityum monoterapisi ile metabolik sendrom gelişme olasılığı diğer tedavilere göre daha düşük gibi görünmektedir. Lityum monoterapisinin kilo alımına yol açabileceği, yine de diabet mellitusu ve bipolar bozukluğu olan hastalarda kan şekeri açısından olumlu olabileceği düşünülebilir. Lityum monoterapisi ve metabolik sendrom arasındaki ilişkinin anlaşılabilmesi için detaylı, ileriye dönük ve geniş örneklemli çalışmalar gereklidir.

Anahtar sözcükler: Abdominal obezite metabolik sendrom, lityum monoterapisi, vücut kitle indeksi

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ABSTRACT:

The prevalence of metabolic syndrome parameters among bipolar disorder outpatients on lithium monotherapy

Objective: Atypical antipsychotics, mood stabilizers or drug combinations, and past depressive episodes have been suggested as risk factors for the development of metabolic syndrome in bipolar affective disorder. Although there are some reports in the literature dealing with the relationship between lithium monotherapy and weight gain, consideration of the relation of lithium monotherapy with metabolic syndrome is lacking. In this study, we aimed to investigate the prevalence of metabolic syndrome in euthymic bipolar affective disorder patients on lithium monotherapy.

Methods: The progress notes between January 2009 and January 2011 in the charts of euthymic patients using lithium monotherapy were screened. According to the NCEP ATP III (Adult Treatment Protocol of the National Cholesterol Education Program) criteria for metabolic syndrome, the following parameters were recorded: triglycerides, high density lipoprotein, fasting glucose levels, waist circumference and blood pressure. The data for patients who had been treated with lithium monotherapy for at least three months were included in the study. The data for patients who had used psychotropic drugs other than lithium, and/or alcohol or other psychoactive substances within three month period were excluded.

Results: The mean age of the patients was 40.47±11.41; the mean age of females was 41.84±12.49 and that of males was 38.88±9.61 (p=0.313). An investigation of first episode type showed that 34 of them had depressive, 29 of them had manic and 2 of them had mixed episodes. The mean duration of illness was 16.70±9.86 and the mean duration of treatment was 16.67±9.90 years. The mean lithium dose was 1160±274 mg/day and the mean blood lithium level was 0.761±0.141 mEq/l. The duration of lithium use was 156.29±117.53 weeks. The mean BMI was 27.67±4.47 kg/m^2 and mean waist circumference was 87.72±12.48 cm and there were no significant differences between gender according to BMI and waist circumference (p=0.173 and p=0.434, respectively). The mean fasting blood glucose level was 87.86±15.53 mg/dl, total cholesterol level was 180.29±47.38 mg/dl, HDL was 38.81±8.62 mg/dl and triglyceride level was 136.57±108.08 mg/dl. Ten patients met the criteria for metabolic syndrome. Nine of these ten patients were females and one was male (χ^2=4.841, p=0.028).

Conclusion: The prevalence of metabolic syndrome seems less frequent in patients with bipolar disorder who are being treated with lithium monotherapy when compared to other treatment modalities. Lithium monotherapy might lead to weight gain, nevertheless it might improve glucose levels in patients with bipolar disorder who have co-morbid diabetes mellitus. Further well designed, prospective studies with larger samples are required to explore the relationship between lithium monotherapy and metabolic syndrome.

Key words: Abdominal obesity metabolic syndrome, lithium monotherapy, body mass index

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INTRODUCTION

Metabolic syndrome (MetS) is a disorder that affects many systems. It is an important risk factor for cardiovascular disease and diabetes (1). Obesity, hyperlipidemia, hypertension, and type 2 diabetes mellitus have been defined as comorbid conditions with significant frequency in patients with bipolar disorder (BD) (1). Weight gain in BD patients is based on many different factors other than the psychotropic drugs that are most often blamed. Weight gain has been suggested to also result from patients spending more than half of their time in the depressive phase or with depressive symptoms, abuse of alcohol, and/or inadequate medical care (2). Although the data on the prevalence of MetS in BD patients are limited, the presence of MetS in BD patients has been studied (3). In two recent studies, one of which has been conducted in our country, the prevalence of MetS in BD patients has been found to be about 30% (1,3). BD patients are treated with mood stabilizers, atypical antipsychotics (AAPs), and sometimes with antidepressant agents for many years. There has been growing interest in the potential metabolic side effects of the AAPs and it is well known that they are associated with weight gain and other MetS components (1,4). In a review article, it has been emphasized that in addition to the AAPs, almost 25% of the patients who are treated with lithium (Li) monotherapy gain weight (5). A follow-up study has shown that the weight gain occurs in the patients receiving Li particularly within the first two years of the treatment and then their weight stabilizes (6). The aim of this study was to conduct a retrospective file review to determine the prevalence of the MetS components in BD patients receiving Li monotherapy.

METHODS

At the end of the clinical visits, the files of outpatients, who had been diagnosed with bipolar mood disorder, were euthymic according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV, TR), who were considered suitable for lithium monotherapy and who were followed by the mood disorder unit, were retrospectively reviewed. The follow-up data were obtained by recording all the relevant information from the files of patients who were seen between January 2009 and January 2011. A sociodemographic data form containing demographic information for the patients, timeline of the course of disease, and information on the following components: triglycerides, high density lipoprotein (HDL), fasting blood glucose (FBG), waist circumference and blood pressure (BP) (7), which are among the metabolic syndrome parameters based on the NCEP ATP III criteria, were recorded during the review of the files. Blood pressure was measured after a 5-minute resting period in the seated position. The waist circumference was measured at the level of the umbilicus. At the time of the review, the file data for patients receiving lithium monotherapy for at least three months were included in the study. The files of patients, who used psychotropics other than lithium within the last three months and then began to receive lithium monotherapy or who reported alcohol or drug use, were excluded from the study. Those patients who receive medication due to their general medical condition other than psychiatric medicines while receiving lithium monotherapy, and those patients who receive 50-100 mg quetiapine, when necessary (e.g. for insomnia) were not excluded.

This data was uploaded into the statistics program and the means and frequencies were reviewed. In the statistical review of the results, the Kolmogorov-Smirnov test was used to determine whether the parameters are normally distributed or not and the Mann-Whitney U, Chi-square and Student's t tests were used. $P<0.05$ was accepted as being statistically significant.

FINDINGS

The mean age of the patients receiving lithium was 40.47±11.41; the mean age of females was 41.84±12.49, and the mean age of males was 38.88±9.61 (p=0.313). There were 27 males and 38 females (41.5% vs. 58.5%) in the study. Thirty-three of the participants (50.5%) were married; 21 of the females and 12 of the males were married, and there was no difference between the genders with respect to the marital statu (χ^2=1.56; p=0.458). Educational background showed no difference between male and female patients (χ^2=4.36; p=0.822). Considering the type of first episode, 34 of the patients had depressive episodes, 29 had manic episodes and 2 of them had mixed

Table 1: Sociodemographic features of the patients

FEATURES	Number	%
Gender		
Male	27	41.5
Female	38	58.5
Marital Status		
Married	33	50.8
Single	32	49.2
Education		
Illiterate	1	1.5
Primary school	31	47.7
High-school	13	20.0
Graduate school	6	9.2
University	14	21.5
Type of first episode		
Depression	34	52.3
Mania	29	44.6
Mixed	2	3.1
Psychotic features		
Present	35	53.8
Not present	30	46.2
Other medical diseases		
Diabetes (DM)	1	1.5
Hypertension (HT)	3	4.6
Goitre	8	12.3
DM + HT	1	1.5
DM + Hyperlipidemia	1	1.5
Other	1	1.5
N/A	50	76.9
Non-psychopharmacological drugs other than lithium		
Anti-diabetic medicine	2	3.1
Thyroid replacement	6	9.2
Anti-hypertensive	3	4.6
Anti-diabetic + Anti-hyperlipidemic	1	1.5
Thyroid replacement +Antitremor	1	1.5
Antitremor	4	6.2
Other	2	3.1
N/A	46	70.8

episodes. With respect to the onset of the disease in males, 16 were depressive, 10 manic and 1 mixed episode, while the rates for females were 18, 19 and 1, respectively. No significant difference was found between the females and males with respect to the type of the first episode (χ^2=1.77; p=0.777). It was found that 35 of the participants had a psychotic episode at any time in their life (14 of the males and 21 of the females (χ^2=1.04; p=0.594)). Fifty of the patients had no additional medical disorder, eight had goiter, three had hypertension, one had diabetes mellitus and hypertension, and one had diabetes mellitus and hyperlipidemia. Seven of the females and one of the males had goiter; no significant difference was found between the genders with respect to additional medical disease (χ^2=7.22; p=0.842). Forty-six of the patients did not receive any medicine other than lithium monotherapy. Seven patients were receiving thyroid hormone, three antihypertensives, one antihyperlipidemic, and five were receiving medicine for tremor developed secondary to lithium. The number of inpatient admissions was a maximum of eight (mean 2±1.81); the number of inpatient follow-ups for manic episodes was a maximum of six (mean 1.50±1.57), for depressive episodes five (mean 0.47±1.06), and for mixed attacks one (mean 0.15±0.124). The time since diagnosis of the disease was 16.70±9.86 years and the treatment period was 16.67±9.90 year. The number of manic episodes were 2.27±2.03, depressive episodes were 2.32±2.95, mixed episodes were 0.13±0.39, and hypomanic episodes were 0.72±1.17 (Table 1). The average lithium dose received by the patients was 1160±274 mg/day and blood levels were 0.761±0.141 mEq/l. The duration of lithium treatment was 156.29±117.53 weeks. The average BMI of the patients was 27.67±4.47 kg/m^2 (F=28.31±5.28 and M=26.76±2.86), and waist circumference was 87.72±12.48 cm (F=89.48±10.33 cm and M=86.87±13.84 cm). There was no significant difference between genders with respect to BMI and waist circumference (p=0.173 and p=0.434, respectively). No significant difference was observed between genders with respect to normal weight, overweight or obesity (χ^2=5.86; p=0.053). The calculated mean fasting blood glucose was 87.86±15.53 mg/dl, total cholesterol level was 180.29±47.38 mg/dl, HDL level was 38.81±8.62 mg/dl, and triglyceride level was 136.57±108.08 mg/dl.

There was no significant difference between genders with respect to receiving medicine other than lithium (χ^2=7.52; p=0.913). The dose of lithium administered to the males was 1286±248 mg/day, and the daily dose of lithium in females was 1073±262 mg, with the males received significantly higher doses of lithium (p=0.002). The fasting blood glucose level in the females was 91.55±15.91 mg/dl, while this level was 82.38±13.81 in the males (p=0.02). There was no significant difference with respect to MetS parameters (HDL, triglyceride, waist circumference, blood pressure) (Table 2). The number of patients with lithium monotherapy that also met at least three of MetS diagnostic criteria was 10, and 2 of these patients met four out of five diagnosis criteria. Of these ten patients, nine were females and one was male (χ^2=4.841, p=0.028).

Table 2: MetS Parameters of the patients receiving lithium monotherapy

	Female (n=38)	Male (n=27)	p
[2]FBG	91.55 ± 15.91 mg/dl	82.38 ± 13.81 mg/dl	0.020*
[2]HDL	39.84 ± 8.45 mg/dl	37.76 ± 8.73 mg/dl	0.346
[1]TRIGLYCERIDES	144.55 ± 113.3 mg/dl min25-max505 mg/dl	126.96 ± 102.8 mg/dl min39-max562 mg/dl	0.604
[2]WAIST CIRCUMFERENCE	86.87 ± 13.84 cm	89.48 ± 10.33 cm	0.434
[1]SYSTOLIC BP	115.53 ± 15.01 mm Hg min90-max160 mm Hg	117.31 ± 17.10 mm Hg min90-max180 mm Hg	0.935
[1]DIASTOLIC BP	70.26 ± 6.36 mm Hg min60-max90 mm Hg	71.92 ± 8.00 mm Hg min60-max100 mm Hg	0.435

[1]Mann Whitney U test and [2]Student's t test,* p<0.05

DISCUSSION

In this retrospective file review study, it was found that the mean BMI of the patients was within the range of overweight, and that the BMI of the females tended to be higher. In addition, it was observed that the fasting blood glucose, total cholesterol, triglyceride, and HDL levels are within normal limits, although the mean waist circumference of the females was higher than the normal limits. It was found that there were ten patients who met at least three of the MetS diagnosis criteria, and of those patients, nine were female and one was male.

In the scientific literature, it has been emphasized that the prevalence of MetS in the general public in our country is 17.9% (8), while this rate rises to 35% in BD patients (1). In our study, this rate was found to be 15.3%. This rate is much lower than the average of the previous study carried out in Istanbul and Gaziantep. However, it has been reported that, within the general public, regional differences may have an impact on the MetS rate, and that the prevalence of MetS is high within the southeastern region (8). Thus, such low number may be caused by the fact that our patients included only those who lived in Istanbul. Another reason for such a low number is that the mean age of the participants in our study is relatively young (mean 40.47±11.41). It has been reported in previous studies that the prevalence of MetS increases, as age increases. For example, the prevalence of metabolic syndrome in 98 individuals with a BD diagnosis and a mean age of 50 was found to be 49% (9). However, the prevalence of MetS in BD patients with a mean age of 35 in our country was found to be 32%, although, the prevalence of MetS in this study was examined in BD patients who had AAPs in their treatment. The number of studies supporting the relation between the use of AAP and MetS incidence has been gradually increasing (1,10). In addition to all these discussions above, it should be noted that the reason for the low MetS prevalence in this study may be Li monotherapy. However, an important deficiency of this study is that it is a cross-sectional study. In addition, looking at the lifestyle, exercising, and dietary habits of BD patients (11) could be more helpful in interpreting the finding of a low prevalence of MetS.

In a cross-sectional study, the prevalence of MetS has been investigated in 170 inpatients with a psychiatric disease (e.g. BD, schizophrenia, depression, schizoaffective disorder, alcoholism, etc.), and significantly more prevalent MetS was found in female patients (12). In our study, nine of ten patients who met the MetS diagnostic criteria were females. In the literature, no data were found on the relation of gender with the prevalence of MetS in BD patients receiving Li monotherapy. In addition to that our study is cross-sectional and the low number of participants makes it difficult to interpret the female gender dominance in the patients under Li monotherapy.

Bipolar Disorder itself has been found to be related to obesity (14) independently of body weight before the onset of the disease (13). In the study carried out by McElroy et al. on 644 outpatients with a BD diagnosis, 58% of the participants were found to be overweight and 26% were found to be obese (15). In our study, the rate of overweight BD patients was found to be 46% and the rate of obesity was found to be 28%, a result which supports the literature data. Mood stabilizers other than lithium are

considered to be related to weight gain. For example, it has been stated in two studies that divalproex is also associated with insulin resistance and weight gain (16,17). For the patients receiving Li monotherapy, significant weight gain has been reported within the period of six years; however, it has been reported that blood glucose levels showed no difference compared to onset of the disease (18). Another insufficiency of our study is that the first body weight of the patients and the impact of the atypical antipsychotics, mood stabilizers or other medication on body weight that may be received before Li monotherapy, are not known. In addition, it has been observed that the mean fasting blood glucose level in our study falls within the normal limits in accordance with the literature. This finding supports the fact that lithium can be safely used in diabetic patients (19).

Consequently, the prevalence of MetS is lower than that observed with other BD treatment modalities in patients with BD receiving Li monotherapy. Moreover, it is considered to be positive to use Li in BD patients with diabetes mellitus in terms of blood glucose. However, it should be noted that Li monotherapy may also cause weight gain. For significantly higher prevalence of MetS in female BD patients receiving Li monotherapy to be understood, detailed and prospective studies with extensive sampling should be conducted.

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