Metabolic Syndrome in Patients with Schizophrenia and Bipolar Disorder in a Community Mental Health Center

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ABSTRACT

Objective: The aim of this study was to determine the frequency of metabolic syndrome (MetS) in patients with schizophrenia and bipolar disorder (BD) receiving antipsychotic (AP) medications.

Methods: A total of 207 patients with schizophrenia and BD, diagnosed according to the DSM-IV criteria and receiving a regular AP treatment, were followed up in the Community Mental Health Center. The MetS was diagnosed according to the diagnostic criteria of the International Diabetes Federation. Patients with MetS were compared to those without it in terms of sociodemographic and clinical characteristics, as well as the AP medications administered.

Results: MetS was detected in 28.5% of patients. The most commonly identified clinical finding was a large waist circumference (61%). Of the clinical characteristics among the patients using AP, a large waist circumference and high blood glucose levels were found to be significantly different. MetS was found to be more common in patients with schizophrenia on AP who used the clozapine monotherapy (18.6%), and in patients with BD who used quetiapine (11.9%). Valproate was found to be more commonly used in patients with BD in whom MetS was detected.

Conclusion: A large waist circumference and high blood glucose levels are the most important follow-up criteria.

INTRODUCTION

Cardiovascular diseases lead to increased morbidity and mortality in patients with schizophrenia and bipolar disorder (BD). Although the studies investigating the coexistence of metabolic disorders with psychiatric diseases are mostly focused on the association of metabolic risk factors such as diabetes and obesity with schizophrenia, there is a similar association for BD as well.^[1-4]

The frequency of MetS in patients with BD is 24.7%—38.3%, [4] whereas it is 13.4%—69.3% [3] in patients with schizophrenia. The etiology of an increased obesity risk and metabolic syndrome in patients with schizophrenia and BD is still unknown. The etiological studies have focused on second-generation antipsychotics (AP), weight gain and subsequent dyslipidemia, and/or metabolic syndrome risk, in addition to psychosocial factors, such as

reduced physical activity, malnutrition, smoking, alcohol, and substance use. [1-6]

MetS is an important disease characterized by increased central obesity, high fasting blood glucose, increased blood pressure, and impaired lipid profiles.^[4]

MetS was first described in the American National Cholesterol Education Program-Third Adult Treatment Panel, revised by the American Heart Association, and the most up-to-date definition was made by the International Diabetes Federation (IDF). The IDF reduced the waist circumference and incorporated the inclusion of two additional measures. [3,4,6]

The most frequent criterion in schizophrenic patients with MetS is a large waist circumference, [2,3,6-9] whereas the least frequent criterion is a high fasting blood glucose (FBG) level. [3,9,10] Glucose intolerance and diabetes

were reported to occur at a rate of 60% in patients with schizophrenia.^[4] De Hert et al. pointed out that the addition of the FBG measure to the assessment of waist circumference in the follow-up of MetS was the method with the highest sensitivity.^[1-3]

The most common AP medications that cause MetS are clozapine, olanzapine, quetiapine, and risperidone; while the use of amisulpride, aripiprazole, sertindole, ziprasidone, haloperidol, and chlorpromazine poses a lower risk. Multiple AP are associated with higher MetS occurrence. [1,3,4,10–13] Weight gain, insulin resistance, hyperlipidemia, impaired glucose tolerance, and hyperinsulinemia associated with the use of lithium and valproate for BD occur in the majority of patients. These risks are lower with carbamazepine and much lower with lamotrigine. [1,4,13]

In this study, we aimed to determine retrospectively the frequency of MetS in patients with schizophrenia and BD who were using AP. Their clinical features were compared to those lacking them, and the medications in both groups were evaluated.

MATERIAL AND METHODS

This study included a total of 207 patients with schizophrenia and BD. The recruits were 18–65 years old and used AP medications on regular basis. They were treated and followed up in the Community Mental Health Center between September 2012 and September 2014. The diagnoses of schizophrenia and BD were made according to the DSM-IV-TR diagnostic criteria.

Diagnosis of metabolic syndrome (MetS)

The diagnosis of MetS was made according to the IDF diagnostic criteria (46), as follows:

- I) Waist circumference (cm) male ≥94, female ≥80;
- 2) Blood pressure (mm/Hg) ≥130/85;
- 3) HDL (mg/dl) male <40, female <50;
- 4) TG (mg/dL) ≥150;
- 5) FBG (mg/dL) ≥100.

On the condition that a large waist circumference is definite, the presence of any other two conditions/measures was sufficient for the MetS diagnosis according to the IDF diagnostic criteria.

In this study, patients with a high blood pressure (i.e., patients taking anti-hypertensives) and those with high blood glucose levels (patients on insulin or hyperglycemic treatment) were considered MetS positive. As a result of all these measurements and assessments, the patients who were diagnosed with MetS meeting the IDF criteria were identified.

This study was conducted in accordance with the Helsinki Declaration and with the approval of the local ethics committee. Subjects were informed, and written consent was obtained.

Statistical assessment

Statistical analyses in this study were performed using the SPSS (Statistical Package for the Social Sciences) 18.0. The continuous variables were expressed as the mean and standard deviation, whereas the categorical variables were expressed as the frequency and percentage. The chisquared test was used to compare the categorical data, while Student's t-test was used to compare the data obtained with inventory. The Levene test was used to investigate the homogeneity of variance. The significance limit was accepted as 0.95 (p<0.05) in all analyses.

RESULTS

Our study group consisted of 133 patients with schizophrenia and 74 patients with BD. Of the patients with schizophrenia, 40 (30%) were female, and 93 (70%) were male, while of the patients with BD, 42 (56.8%) were female, and 32 (43.2%) were male. The mean age of the patients with schizophrenia was 43.40±7.46 years, while that of the patients with BD was 45±11.08 years. A statistically significant difference was detected in both groups in ad-

Table 1. Comparison of sociodemographic data and treatments for schizophrenia and bipolar disorder

	Schizophrenia disorder (n=133)		Bipolar (n=74)		χ²	р
	n	%	n	%		
Sex					14.1	0.00
Male	93	44.9	32	15.5		
Female	40	19.3	42	20.3		
Marital state					3.45	0.01
Married	43	20.8	33	15.9		
Single	90	43.4	41	19.8		
Employment					4.18	0.24
Working	19	9.2	16	7.7		
Retried						
person	99	47.8	52	25.1		
Unemployed	15	7.3	6	2.9		
Antipsychotic (AP)					45.5	0.00
Atypical AP	105	50.7	66	31.9		
Typical AP	28	13.5	8	3.9		
Mood stabilizer					38.08	0.00
Valproate			48	64.9		
Lithium			14	18.9		
Carbamazepine			6	8.1		
Lamotrigine			6	8.1		
	Median±SD		Median±SD		t	р
Body mass index	32.12	32.12±7.81		9±6.17	0.28	0.99
Age	43.40±7.46		45±11.08		-2.67	0.01

268 South. Clin. Ist. Euras.

 Table 2.
 The metabolic syndrome ratio and a positive clinic criterion percentage of patients

	Patients	%	Male	%	Female	%	χ^{2}	р
Metabolic syndrome	59	28.5	33	15.9	26	12.6	2.67	0.1
Metabolic syndrome schizophrenia	32	54.2	18	56.2	14	43.8		
Metabolic syndrome bipolar disorder	27	45.8	15	55.5	12	44.5		
Waist circumference	126	60.8	63	30.4	63	30.4	14.52	<0.01
Low high-dansity lipid	95	45.9	56	27.1	39	18.8	0.15	0.19
High triglycerides	105	50.7	67	32.3	38	18.4	0.54	0.46
High blood pressure	51	24.6	36	17.3	15	7.3	0.56	0.45
High fasting blood glucose	55	26.6	30	14.5	25	12.1	0.29	<0.05

 $[\]chi^2$: Chi-squared test, p<0.05.

Table 3. Comparison of a positive clinic criterion on schizophrenia and bipolar disorder with metabolic syndrome

	Schizophrenia	%	Bipolar disorder	%	$\chi^{\mathbf{z}}$	р
Waist circumference	31	52.5	26	44. I	0.01	1
Low high-density lipid	26	44.I	16	27.1	3.45	0.06
High triglycerides	28	47.5	25	42.4	0.41	0.67
High blood pressure	16	27.1	14	23.7	0.02	0.88
High fasting blood glucose	22	37.3	17	28.8	0.21	0.64

 $[\]chi^2$: Chi-squared test, p<0.05.

vanced age. 43.75% percent of patients with schizophrenia and 55.6% of patients with BD were married, and 47.8% of patients with schizophrenia and 25.1% of patients with BD were retired due to disability. A significant difference was found in terms of the male gender in patients with schizophrenia, in terms of the female gender in patients with BD, and in terms of the MetS development among single patients in both disease groups (p<0.05). MetS was significantly different as a risk factor in both groups for those who were on AP and in the BD group who were on mood stabilizers (MS) (Table I). The risk of developing

Table 4. Comparison of antipsychotic treatment of schizophrenia and BD with MetS

	Schizophrenia (n=32)		BD (n=27)		χ²	р
	n	%	n	%		
Clozapine	П	18.6	0	0	18.57	0.01
Olanzapine	8	13.6	2	3.4		
Risperidone	8	13.6	0	0		
Quetiapine	7	11.9	7	11.9		
Aripirazole	4	6.8	5	8.5		
Haloperidol	2	3.4	1	1.7		
Amisulpride	- 1	1.7	0	0		
Paliperidone	2	3.4	0	0		
Zuclopenthioxle	0	0	-1	1.7		

 $[\]chi^2$: Chi-squared test, p<0.05. MetS: Metabolic syndrome; BD: Bipolar disorder.

MetS for patients with schizophrenia and BD was highest 20.33±9.16 years after the onset of the disease.

MetS was detected in 28.5% of our patients according to the IDF criteria. Of these, 32 (54.2%) had schizophrenia, and 27 (45.8%) had BD. The most commonly detected criterion was a large waist circumference (60.8%), whereas the least common criterion was high blood pressure (24.6%). The frequency of large waist circumference was the same in both men and women (p<0.01). Among the clinical parameters, a large waist circumference and high FBG were found to be significantly different (Table 2).

There was no statistically significant difference found in patients for clinical parameters of MetS (Table 3).

The most commonly used medications were clozapine (18.6%) in patients with schizophrenia and quetiapine (11.9%) in patients with BD, respectively. A significant difference was found between the MetS and AP use in both groups (Table 4). The most commonly used MS for the diagnosis of BD was found to be valproate (64.9%).

DISCUSSION

MetS is a major cause of morbidity and mortality in chronic mental diseases. MetS was detected in 28.5% of patients in the present study. 54.2% of the patients with MetS had schizophrenia, and 45.8% had BD. The prevalence of adult obesity and MetS in chronic mental diseases in the United States was reported to have increased from 23% to 31%. [3.2,14] In a study conducted in Turkey, the rate of MetS was reported to be 14.2% in the Black Sea region and 17.2%

in the whole country.[15] Another study reported the rate of MetS as 27% in patients with schizophrenia in Turkey.[16] MetS was shown to be 32% in the inpatient patients with schizophrenia.[3,4] The prevalence of MetS was found to vary between 19.4% and 68% in patients with schizophrenia and between 22% and 30% in patients with BD.[1] It was found that the first episodes of schizophrenic patients who did not take psychotropic drugs had a higher prevalence of impaired FBG, higher insulin resistance, and increased insulin levels than the control group without schizophrenia. Patients with schizophrenia are either treated or not, and the prevalence of diabetes is three times more frequent in patients with schizophrenia than in the general population. It has been stated that a high MetS prevalence in patients with schizophrenia can be related to disease itself, heredity, weight gain, age increase, hypertriglyceridemia, hypertension, ethnicity, lack of physical activity, poor diet and drugs leading to diabetes, are considered a risk factor for the development of type 2 diabetes. The disease itself has been shown to increase the rate of diabetes in drug-naïve patients with schizophrenia. [2,4,17] It is emphasized that negative psychotic symptoms, cognitive impairment, sedating effects of AP drugs, and decreased self-care in schizophrenia patients lead to a life-threatening lifestyle that leads to MetS.[1-4] These data indicate that MetS is an important health problem, especially for patients with schizophrenia and BD. Data pertaining to the prevalence of MetS in patients with schizophrenia is consistent in different studies, but a higher prevalence of MetS in patients with BD in this study compared to other studies emphasizes the necessity for the evaluation of BD patients in this respect in future studies.

Gender-based MetS differences varied for patients with both chronic psychiatric disorders. The MetS ratio was found to be higher in women with chronic psychiatric disorders in the United States. The frequency of MetS in Turkey varied from one study to another, and it was higher in women overall.^[4] The prevalence of MetS in patients with schizophrenia, which was made according to the Clinical Antipsychotic Intervention Activity Study (CATIE), was found to be higher (51.6%) in women than men (36%). [4] Kaya et al. (2009) reported similar findings in their study in Turkey.^[18] There are also studies indicating that there is no difference in terms of the MetS development and gender in patients with schizophrenia^[2,3] and with BD.^[13]

While there are studies showing that the advanced age and disease duration constitute a risk factor for MetS in psychiatric patients, [1,2,4,8,10] there are also studies that found no difference in terms of age and diseases duration. [3,4,18] In this study, MetS was more common in older male patients with schizophrenia and female patients with BD. Poor lifestyle was demonstrated to lead to the development of MetS in patients with schizophrenia and BD. [2,17,19] A higher frequency of MetS in patients who were single in our study suggests that the lifestyle factors mentioned are effective. MetS was more common in the subchronic (10–20 years) period of diseases in schizophrenia and BD in our study.

These findings are supported by other studies.[1-3] The most common MetS criterion observed in our study was a large waist circumference, which was the same (30.4%) for both genders (60.8%). Obesity, especially abdominal obesity, was reported to be an important problem in people with a chronic mental disease. Compared to normal population, obesity was reported to be 2.8-3.5 times higher in patients with schizophrenia and 1.2-1.5 times higher in patients with BD. When MetS was assessed according to the IDF criteria, the waist circumference measurement was reported to be the main criterion. Our study found that there was a significant association between the large waist circumference with abdominal obesity in both disease groups, supporting these findings. Studies examining the association of MetS with gender indicate a wide variability in MetS research.[1] Numerous studies showed that a large waist circumference was more common in females.[2,3,7,9,10] A number of factors ranging from poor living conditions to medical treatment were investigated in etiological studies on obesity.[1-3,8,9,13,16] The fact that abdominal obesity was high in both men and women in our study suggests that abdominal obesity is also an increasing problem for men. The fact that a high blood pressure was the least frequent factor in our study, as it was in other studies, supports these findings.[3] The FBG measurement in addition to the waist circumference for the follow-up of MetS was suggested to be more accurate.[1-3,14,17,19,20] A high incidence of FBG in patients with MetS confirms this in our study.

One of the most important reasons for the development of MetS is the AP treatment in patients with chronic mental diseases. MetS formation differs between atypical APs. MetS shows a very high level with clozapine and olanzapine; high levels with quetiapine, zotepine, chlorpromazine, and thioridazine; medium levels with risperidone and sertindolle; and low levels with ziprasidone, amisulpride, aripiprazole, haloperidol, fluphenazine, pimozide, and molindone.[3-6,12,21-27] MetS occurs more as a result of the use of multiple AP. Sarısoy et al. found no difference in terms of the used AP group.[16] In addition to having unique receptor-binding features, their heterogeneous receptor-binding properties are also involved in the occurrence of the metabolic side effects caused by atypical APs. A dopamine/ serotonin/histamine neurotransmission interaction is thought to have a regulatory effect on the appetite. The lateral hypothalamus is a critical anatomical region for the regulation of body weight; dopamine is known to be able to inhibit the appetite-reducing effect on this site with AP drugs.^[28] It has been recognized that the 5-HT2A receptor has a regulatory effect on metabolic syndrome and physical activity. However, 5-HT2A not only provides the energy balance in the brain, but it also regulates the effects of insulin on the striated muscle tissue. The serotonergic system, especially the 5-HT 2C antagonism, increases the food intake effect.[29] A significantly lower risk of developing MetS has been observed with aripiprazole compared with the other atypical APs, especially olanzapine. Aripiprazole is a partial agonist at the D2 dopamine and 5HTIA serotonin receptors and an 270 South. Clin. Ist. Euras.

antagonist at 5HT2A serotonin receptors, whereas olanzapine is an antagonist at the D2 dopamine, 5HT2A and 5HT2C serotonin, M1 muscarinic, and histamine-1 receptors. [29,30] A 26-week-long study of aripiprazole showed no clinically significant change in the FBG levels.[3] Our study revealed that the risk of MetS increases in patients with schizophrenia who were on clozapine as an AP, in patients with BD who were on quetiapine, and in both groups who were on multiple AP medications. Numerous studies reported an association between the AP use and weight gain, which has been studied more frequently in patients with schizophrenia.[10-12,15,16,18] and less frequently in patients with BD.[1,13,19] With respect to MetS, the AP use and weight gain was similar in patients with BD.[1,13,19,26,27,31] Our study supported an increased risk of clozapine in the development of MetS, and more caution should be exercised with the use of quetiapine. Among the MS, valproate and lithium were reported to be the strongest, carbamazepine and gabapentin were moderate, and lamotrigine and oxcarbazepine were the weakest MetS risk factors for weight gain.[1,25,32] A study conducted in Turkey reported that the risk of developing MetS with lithium monotherapy was lower compared to other treatments.[31] Supporting these findings, our study found that the risk for MetS was higher in patients with valproate as a MS in BD.

CONCLUSION

MetS is an important health issue in patients with schizophrenia and BD treated by APs. The follow-up of waist circumference and FBG measurements are more important for MetS. Clozapine and quetiapine among APs and valproate among MSs are the medications that increase the risk of MetS. To obtain more accurate information about MetS, clinical parameters, and treatment, studies with larger samples need to be conducted.

Ethics Committee Approval

Approved by the local ethics committee.

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: K.S.K., B.B.; Design: K.S.K., B.B.; Data collection &/or processing: K.S.K., H.A., F.A.; Analysis and/or interpretation: K.S.K., B.B.; Literature search: K.S.K., H.A., F.A.; Writing: K.S.K., B.B.; Critical review: K.S.K., B.B., H.A., F.A.

Conflict of Interest

None declared.

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Toplum Ruh Sağlığı Merkezinde Takip Edilen Şizofreni ve İki Uçlu Bozukluk Hastalarında Metabolik Sendrom

Amaç: Bu çalışmada, antipsikotik ilaçlarla tedavi altında olan şizofreni ve iki uçlu bozukluk (İUB) hastalarında metabolik sendrom (MetS) sıklığının saptanması amaçlanmıştır.

Gereç ve Yöntem: DSM-IV tanı kriterlerine göre tanısı konan, Toplum Ruh Sağlığı Merkezi'nde takip edilen, düzenli antipsikotik tedavi alan 207 şizofreni ve İUB hastaları çalışmaya alındı. MetS tanısı Uluslararası Diyabet Fedarasyonu tanı kriterlerine göre kondu. MetS tanısı konan hasta grupları arasında sosyodemografik, klinik özellikler ve uygulanan antipsikotik ilaçlar açısından karşılaştırma yapıldı.

Bulgular: Hastaların %28.5'inde MetS saptandı. En sık saptanan klinik bulgu, bel çevresi genişliği (%61) idi. Antipsikotik kullanan hastalarda klinik özellikler arasında bel çevresi genişliği ve kan glukoz seviyesi yüksekliği anlamlı olarak farklı bulundu. Antipsikotik kullanan şizofreni hastalarında monoterapilerde klozapin (%18.6), İUB hastalarında ketiyapin (%11.9) kullanımında MetS daha sık olarak bulundu. MetS saptanan İUB hastalarında duygudurum düzenleyici ilaç olarak valproatın daha sık kullanıldığı saptandı.

Sonuç: Bel çevresi genişliği ve kan şekeri yüksekliği takipte en önemli kriterlerdir.

Anahtar Sözcükler: Antipsikotik ilaçlar; ikiuçlu bozukluk; klinik özellikler; metabolik sendrom; şizofreni.