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Correlation of Metabolic Syndrome with Serum BDNF, Vitamin B12 And Folate In Schizophrenic Patients.

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ABSTRACT

The aim of this study is to evaluate the correlation of vitamin B12, folate and serum (brain derived neurotrophic factor) BDNF levels with anthropometric ((body mass index (BMI) and waist circumference), metabolic (glucose, insulin, insulin resistance, HbA1c and lipid profile) and psychopathological (positive and negative syndrome scale (PANSS)) parameters. Anthropometrical parameters (weight, height, BMI and waist circumference), systolic and diastolic blood pressure, serum glucose, HDL, LDL, triglyceride, total cholesterol, HbA1c, insulin, vitamin B12, folate, HOMA-IR and serum BDNF values of 64 schizophrenic patients and 54 healthy individuals, whose informed consent was obtained, and were measured using the sandwich ELISA (enzyme-linked immune sorbent assay) method. The PANSS was used to evaluate the patients. Serum BDNF and vitamin B12 levels were found to be significantly lower in 27 (42.18%) schizophrenic patients with the diagnosis of metabolic syndrome (MetS) when compared to the other schizophrenic patients (p<0.001 and p=0.012, respectively). Significant negative correlations were found among BDNF, folate and vitamin B12 (r= -0.651, p<0.001; r= -0.324, p=0.009; r= -0.646, p<0.001, respectively) with PANSS-negative syndrome scale, between BDNF and vitamin B12 (r= -0.523, p<0.001; r= -0.313, p=0.012, respectively) with PANSS-positive syndrome score and between BDNF and vitamin B12 (r= -0.381, p=0.002; r= -0.268, p=0.032, respectively) with PANSS-total syndrome scalee. In patients with schizophrenia, vitamin B12 level and BDNF were found to be positively correlated. Lower serum BDNF and vitamin B12 levels in schizophrenic patients may be correlated with a risk of the development of MetS and increased psychotic symptoms. In addition, folate deficiency may be associated with a higher PANSS-negative syndrome scale, especially in schizophrenic patients. Psychotic symptoms might be more intense in schizophrenic patients with MetS compared to schizophrenic patients without MetS

Keywords: Schizophrenia, Metabolic syndrome, BDNF, PANSS, vitamin B12, folate.

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INTRODUCTION

Metabolic syndrome (MetS), which is progressively increasing in incidence worldwide, is a health issue with a high mortality and morbidity due to complications. Its characteristic properties are dyslipidemia, abdominal obesity, increased blood pressure and glucose intolerance. It has been reported in studies that the incidence of the development of MetS is quite high among schizophrenic patient groups (1). Although there are some studies reporting significant positive correlation between PANSS, which is among the psychopathological measurement methods, and BMI, waist circumference, TC, TG, HDL and glucose levels measurements, which are among the metabolic syndrome criteria, data are rather scarce regarding this issue (2).

BDNF is a polypeptide of the neurotrophic factor family that is synthetized by the hippocampus and cortex neurons, which provides the development, differentiation and survival of neurons. The BDNF and TrkB receptor expressions were demonstrated to be decreased in the prefrontal cortex, dentate gyrus, hippocampus, cerebrospinal fluid, plasma and serum of schizophrenic patients (3). In addition, although there are some studies exploring the correlation between a PANSS value and serum BDNF levels, data are insufficient for a clear conclusion (2).

In addition to its neuropsychiatric effects, BDNF has been demonstrated to be a regulator in energy homeostasis and this was demonstrated to be correlated with its expression in the hypothalamus as well as the ventromedial, dorsomedial and paraventricular nuclei. Although studies have been published reporting decreased serum BDNF levels in patients with MetS, some controversial information about BDNF's diabetic and lipidemic effects have also been reported. Data on the association of MetS and BDNF in schizophrenic patients are quite scarce (4).

Vitamin B12 and folate play a role in the single carbon transfer that is required for the production of monoamine neurotransmitters, phospholipids and nucleotides. Considerable research exists that demonstrates the deficiency of vitamin B12 and folate in patients with schizophrenia. Impairment of single carbon metabolism and DNA methylation have been demonstrated in vitamin B12 and folate deficiency to the development of neuropsychiatric diseases associated with these deficiencies have been reported (5,6). Additionally, BDNF gene expression, which plays a major role in neuron development and differentiation, has been known to increase with vitamin B12 (7). According to some studies, the detected correlation between vitamin B12 and PANNS demonstrates that vitamin B12 levels effect the psychopathology of the schizophrenic patient (8).

Although there have been publications demonstrating that obesity, impairment of lipid profile and metabolic syndrome is related to vitamin B12 deficiency, as is BDNF, and that the risk of MetS increases with vitamin B12 deficiency; however, there are no data demonstrating this association in schizophrenic patient groups (9,10). Although the vitamin B12 and serum BDNF levels have been evaluated separately, there is no published study evaluating these parameters and explaining their connections to MetS and psychopathological measurements.

The aim of this study is to evaluate the correlation of serum BDNF, vitamin B12 and folate levels with anthropometric, metabolic (glucose, insulin, insulin resistance, HbA1c and lipid profile) and psychopathological parameters in schizophrenic patients compared to a control group. In addition, the correlation between serum BDNF and vitamin B12 affects the patients with schizophrenia and MetS was evaluated.

SUBJECTS AND METHODS

This study included 64 voluntary patients, who were diagnosed at the Antalya Education and Research Hospital psychiatry outpatient clinic with schizophrenia and schizoaffective disorder, according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, IV: Edition) diagnostic criteria, that were followed-up for at least two years and 54 healthy individuals in the control group, between the ages of 18–65 years old (11). Informed consent was obtained from both patient and control groups. Individuals with a diagnosis of neurological diseases, psychosis and atypical psychosis, mental retardation and accompanying eating disorder and individuals with substance and alcohol use were excluded from the study. A socio-demographical data form was completed for each patient that included age, gender, marital status, level of education, smoking and

drug usage information. The study complied with the Declaration of Helsinki, and was approved by institutional ethics committee.

Anthropometrical data (body weight, height and waist circumference) and systolic and diastolic blood pressures of the patient and control groups were measured. Body weight was measured with clothes on and height was measured without shoes and then the body mass index (BMI) was calculated. Waist circumference was measured just above the iliac crests with the patient in an erect position. Systolic and diastolic blood pressures were measured at the right and left arms two times with two minutes intervals from individuals who did not smoke or consume caffeine 30 minutes prior and who rested in the sitting position for at least five minutes. The means were later calculated.

Blood was taken from the individuals included in the study from the antecubital veins for laboratory analyzes following a 12-hour fasting period. Routine parameters of insulin, vitamin B12 and folate were measured using chemiluminescence immunoassay (CLIA) in the UniCel DXI 800 Access Immunoassay System auto analyzer and glucose, HDL, (high-density lipoprotein cholesterol), LDL (low-density lipoprotein cholesterol), triglyceride (TG) and total cholesterol (TC) were measured in an AU 5800 auto analyzer (Beckman Coulter) using spectrophotometric methods. HbA1c was measured using a Tosoh HLC-723 GHb G7 equipment with the HPLC method and HOMA-IR was calculated using a formula (insulin (µU/ml) x glucose (mg/dl) / 405) (12). Serum BDNF was measured using the ELISA (Yh-Biosearch BDNF ELISA kit) method. Intra-assay and inter-assay coefficients of variation values were CV<10% and CV<12%, respectively. MetS patients were evaluated in terms based on the IDF (International Diabetes Federation) diagnostic criteria. According to the IDF criteria, abdominal obesity (waist circumference ≥ 94 cm in males and ≥ 80 cm in females) and at least two out of four following criteria should be present: triglyceride ≥ 150 mg/dl, HDL < 40 mg/dl in males and < 50 mg/dl in females, blood pressure ≥ 130/85 mmHg, fasting blood sugar ≥ 100 mg/dl or diagnosis of Type 2 diabetes mellitus (DM).

A semi-structured PANNS interview, which included a 30-item and 7-point violence evaluation developed by Kay et al. (13), was used to evaluate the patients. Of the 30 psychiatric parameters, seven comprised the positive syndromes subscale, seven in the negative syndromes subscale and the remaining 16 were in the general psychopathology subscale. Kostakoglu et al. carried out the Turkish reliability and validity study of the scale (14). During the follow-up with the patients, in case of a detection of at least one the symptoms (i.e. auditory hallucination), the related symptom was accepted as a positive symptom.

Statistical Analysis

Data were analyzed by using PASW 18 (SPSS/IBM, Chicago, IL, USA). For the description of the sample, descriptive statistics such as frequency distribution, mean and standard deviation were used. In cases where parametric test hypothesis were confirmed, the average difference between the two independent groups was analyzed using “Student t test” and the differences between over two groups was compared using “variance analysis”. In cases where parametric test hypothesis could not be confirmed, nonparametric alternatives of these tests, namely “Mann–Whitney U” and “Kruskal–Wallis” tests were used. In addition, correlations between the continuous parameters were analyzed using Pearson and Spearman correlation coefficients. Categorical variables were analyzed using “chi-square test of significance” or "Fisher's exact test".

To define the differences, 95% level of significance (or α=0.05 error) was used.

RESULTS

Sociodemographic and clinical characteristics of the patient and control groups included in the study are shown in Table 1.

BMI, waist circumference, total cholesterol, triglyceride, insulin, HOMA-IR and HbA1c were significantly high in schizophrenic patients when compared to the control group, while HDL and vitamin B12 levels were found to be significantly lower (Table 2, Figure 1).

Among the 64 schizophrenic patients, 27 (42.18%) were diagnosed as MetS according to the IDF (International Diabetes Federation). The BMI, waist circumference, glucose, triglyceride, insulin, HOMA-IR,

HbA1c, PANSS-N (negative syndrome scale) and PANSS-P (positive syndrome scale) in schizophrenic patients with a diagnosis of MetS were significantly higher compared to the group without a diagnosis of MetS, while serum vitamin B12 and BDNF levels were found to be significantly lower (Table 3).

In the schizophrenic patient group, PANSS-negative syndrome scale and waist circumference, glucose, triglyceride, insulin, HOMA-IS and HbA1c were statistically significantly positively correlated. PANSS-negative syndrome scale and HDL, LDL, vitamin B12, folate and BDNF were significantly negatively correlated. PANSS-T (total syndrome scale) and waist circumference, insulin and HOMA-IR was statistically significantly positively correlated, while it was significantly negatively correlated with vitamin B12 and BDNF (Table 4).

In the schizophrenic patient group, vitamin B12 levels were significantly negatively correlated with systolic blood pressure, diastolic blood pressure, triglyceride, insulin, HOMA-IR and HbA1c and significantly positively correlated with HDL and BDNF. Folate levels were positively significantly correlated with BMI and HDL. In the schizophrenic patient group, BDNF was negatively correlated with BMI, waist circumference, systolic blood pressure, diastolic blood pressure, glucose, total triglyceride, insulin, HOMA-I and HbA1c. In the same group, BDNF and HDL, LDL and vitamin B12 were positively correlated (Table 5). A significant positive correlation was found between smoking and serum BDNF levels in the patient group (p=0.045).

Table 1. Sociodemographic characteristics of the patient and the control groups.

	Patient group n=64	Control group n=54
Age range (years)	20-57	23-61
Age, mean ±SD	38.25±7.69	36.87±3.59
Gender (n (%))		
Female	28 (42.6)	23 (43.8)
Male	36 (57.4)	31 (56.3)
Marital status (n (%))		
Single	36 (56.25)	14 (25.92)
Divorced,separate	10 (15.63)	7 (12.96)
Married	18 (28.12)	33 (61.12)
Education (n (%))		
Literate	10 (15.62)	7 (12.96)
Primary school graduate	20 (31.24)	11 (20.37)
Secondary school, lycée graduate	22 (34.38)	14 (25.93)
University graduate	12 (18.76)	22 (40.74)
Smoking (n (%))		
Yes	42 (65.60)	26 (48.10)
No	22 (34.40)	28 (51.90)
Duration of disease (year) (mean±SD)	12±7.32	
Drug therapy (n (%))		
Atypical antipsychotic	45 (70.31)	
Typical antipsychotic	9 (14.06)	
Typical/atypical antipsychotic	10 (15.63)	
Type of schizophrenia (n (%))		
Paranoid	48 (75.00)	
Disorganized	5 (7.81)	
Undifferentiated	5 (7.81)	
Residual	6 (9.38)	

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Table 2: Anthropometrical and biochemical parameters in schizophrenic patient group and control group. Statistically significant associations are represented in bold.

	Schizophrenia group (n=64) Mean±SD	Control group (n=54) Mean±SD	p
Age (years)	38.25±7.69	36.87±3.59	0.400
BMI (kg/m^2)	29.35±2.35	24.74±2.34	**<0.001****
Waist circumference (cm) Male Female	95.32±9.18 98.12±8.71 91.27±8.42	91.79±4.88 94.11±3.55 88.72±4.71	**0.013*** **0.003**** 0.051
Systolic blood pressure (mm Hg)	122.54±6.92	120.75±8.92	0.222
Diastolic blood pressure (mm Hg)	80.84±6.04	79.07±5.75	0.209
Glucose (mg/dl)	101.48±20.04	95.66±17.78	0.054
TC (mg/dl)	193.45±36.08	161.53±20.22	**<0.001****
TG (mg/dl)	171.67±97.17	138.50±26.66	**0.012***
HDL (mg/dl) Male Female	43.64±8.96 44.11±9.32 42.70±8.53	47.53±7.81 46.9±7.46 48.3±8.33	**0.007**** 0.096 **0.029***
LDL (mg/dl)	114.20±32.92	106.42±21.53	0.054
Insulin (µU/ml)	8.50±2.30	6.85±2.11	**<0.001****
HOMA-IR	2.17±0.87	1.69±0.80	**<0.001****
Hb A1C (%)	6.05±1.73	2.96±0.86	**<0.001****
Vitamin B12 (pg/ml)	225.47±109.20	318.27±106.94	**<0.001****
Folate (ng/ml)	8.94±2.88	9.37±2.44	0.281
Serum BDNF (pg/ml)	2549.1±150.08	2917.9±83.62	0.118

* Significant at level p<0.05 ** Significant at level p<0.01
BMI: body mass index, TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein- cholesterol, and HOMA-IR: homeostasis model assessment of insulin resistance, BDNF: brain-derived neurotrophic factor,

Table 3: Comparison of anthropometric and biochemical parameters between the subgroups of schizophrenic patients with and without metabolic syndrome. Statistically significant associations are shown in bold.

	Whitout MetS (n=37) ort±ss	Whit MetS (n=27) ort±ss	p değeri
Atypical Antipsychotic (%)	21 (56.8)	15 (55.6)	
Typical Antipsychotic (%)	6(16.2)	5 (18.5)	
Combined Antipsychotic (%)	10(27)	7(25.9)	
Age (year)	37±8	39±8	0.354
BMI (kg/m^2)	28.56±1.89	30.09±2.43	**0.006**
Waist circumference (cm)	92.22±8.99	99.56±7.75	**0.001**
Systolic blood pressure (mm Hg)	121±7	124±7	0.107
Diastolic blood pressure (mm Hg)	80±5	82±7	0.369
Glucose (mg/dl)	94±15	112±22	**<0.001**
TK(mg/dl)	189±32	199±40	0.269
TG (mg/dl)	132±51	226±118	**<0.001**
HDL (mg/dl)	45±9	42±9	0.168

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LDL (mg/dl)	119±25	108±41	0.215
Insulin (µU/ml)	7.45±1.30	9.94±2.61	**<0.001**
HOMA-IR	1.73±0.42	2.78±0.97	**<0.001**
Hb A1C (%)	5.37±1.22	6.98±1.90	**<0.001**
Vitamin B12 (pg/ml)	254.22±116.38	186.08±85.76	**0.012**
Folate (ng/ml)	9.00±2.58	8.85±3.30	0.842
Serum BDNF (pg/ml)	3293.7±126.79	1419.3±111.82	**<0.001**
PANSS-N	16.11±1.73	18±1.80	**<0.001**
PANSS-P	15.51±3.42	21.85±4.73	**<0.001**
PANSS-T	70.16±14.20	76.48±16.10	0.161

BDNF: brain-derived neurotrophic factor, BMI: body mass index, TC: total cholesterol, TG: triglyceride, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol, and HOMA-IR: homeostasis model assessment of insulin resistance. PANSS-N: PANSS-Negative syndrome scale, PANSS-P: PANSS-Positive syndrome scale, PANSS-T: PANSS-Total syndrome scale.

Table 4: Correlations of metabolic parameters with PANSS score. Statistically significant associations are indicated in bold.

	PANSS-N		PANSS-P		PANSS-T	
	R	P	R	P	R	P
BMI (kg/m^2)	0.142	0.264	0.114	0.368	0.084	0.508
Waist circumference (cm)	0.427	**<0.001**	0.394	**0.001**	0.354	**0.004**
Systolic blood pressure (mm Hg)	0.194	0.124	0.289	0.020	0.126	0.320
Diastolic blood pressure (mm Hg)	0.169	0.183	0.179	0.158	0.067	0.601
Glucose (mg/dl)	0.571	**<0.001**	0.435	**<0.001**	0.202	0.109
TK(mg/dl)	-0.106	0.404	0.078	0.540	0.097	0.447
TG (mg/dl)	0.329	**0.008**	0.369	**0.003**	0.135	0.289
HDL (mg/dl)	-0.302	**0.015**	-0.335	**0.007**	-0.206	0.103
LDL (mg/dl)	-0.338	**0.006**	-0.151	0.233	0.013	0.921
Insulin (µU/ml)	0.544	**<0.001**	0.517	**<0.001**	0.324	**0.009**
HOMA-IR	0.629	**<0.001**	0.518	**<0.001**	0.286	**0.022**
Vitamin B12 (pg/ml)	-0.646	**<0.001**	-0.313	**0.012**	-0.268	**0.032**
Folate (ng/ml)	-0.324	**0.009**	-0.243	0.053	-0.121	0.341
Hb A1C (%)	0.529	**<0.001**	0.437	**<0.001**	0.245	0.051
Serum BDNF (pg/ml)	-0.651	**<0.001**	-0.523	**<0.001**	-0.381	**0.002**

PANSS-P: Positive and Negative Syndrome Scale for schizophrenia-Positive syndrome score, PANSS-N: Positive and Negative Syndrome Scale for schizophrenia-Negative syndrome score, PANSS-T: Positive and Negative Syndrome Scale for schizophrenia-Total syndrome score.

Table 5: Comparison of vitamin B12, folate and BDNF values with other parameters in schizophrenic patients. Statistically significant associations are represented in bold.

	Vit B12		**Folat**		**BDNF**	
	R	p	R	P	R	p
BMI (kg/m^2)	-0.207	0.101	0.262	**0.036**	-0.301	**0.016**
Waist circumference (cm)	-0.244	0.052	-0.015	0.907	-0.538	**<0.001**
Systolic blood pressure (mm Hg)	-0.352	**0.004**	-0.087	0.494	-0.399	**0.001**
Diastolic blood pressure (mm Hg)	-0.268	**0.032**	-0.060	0.636	-0.289	**0.021**
Glucose (mg/dl)	-0.174	0.169	-0.028	0.828	-0.488	**<0.001**
TK(mg/dl)	0.076	0.551	-0.100	0.429	0.026	0.837
TG (mg/dl)	-0.322	**0.010**	0.036	0.775	-0.581	**<0.001**
HDL (mg/dl)	0.491	**<0.001**	0.306	**0.014**	0.368	**0.003**
LDL (mg/dl)	0.173	0.172	-0.181	0.153	0.276	**0.027**

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Insulin (µU/ml)	-0.475	**<0.001**	-0.179	0.157	-0.709	**<0.001**
HOMA-IR	-0.410	**0.001**	-0.123	0.333	-0.714	**<0.001**
Hb A1C (%)	-0.250	**0.046**	0.061	0.634	-0.481	**<0.001**

BDNF: brain-derived neurotrophic factor, BMI: body mass index, TC: total cholesterol, TG: triglyceride, HDL-c: high-density lipoprotein-cholesterol, LDL-c: low-density lipoprotein-cholesterol, and HOMA-IR: homeostasis model assessment of insulin resistance.

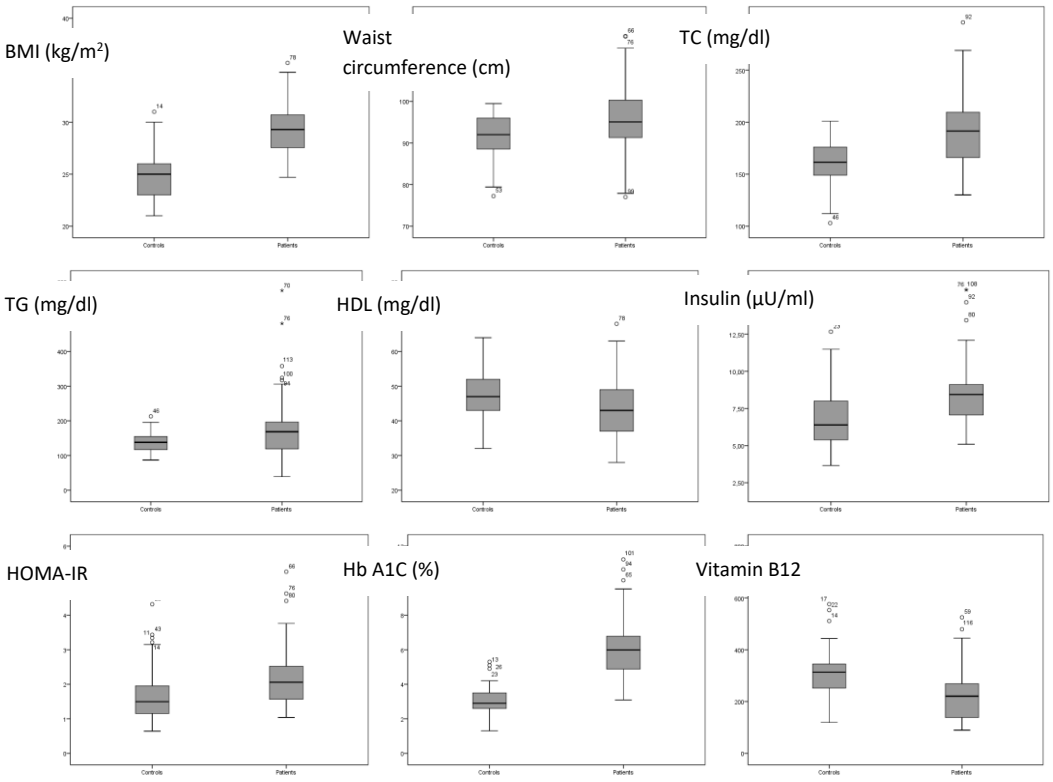

Figure 1: The comparison of statistically significant parameters in schizophrenic patients and the control group.

BMI: body mass index, TC: total cholesterol, TG: triglyceride, HDL: high-density lipoprotein-cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance.

DISCUSSION

Observation of the significantly higher levels of BMI, waist circumference, TC, TG, insulin, HOMA-IR and HbA1c in the schizophrenic patient group compared to the control group demonstrates that the risk of MetS development is higher in schizophrenic patients compared to the control group. In studies on this topic, the incidence of MetS has been reported to vary greatly, approximately 5.6–63% in schizophrenic patients (15). The most comprehensive research on this issue, namely the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study reported that one-third of schizophrenic patients had MetS according to the National Cholesterol Education Program Adult Treatment Panel description (16). In a 2015 study carried out in Egypt on 100 schizophrenic patients, 31% of the patients were diagnosed with MetS (2). In this present study, 27 out of 64 schizophrenic patients (42%) were found to have MetS. This might be due to the fact that the hospital where this present study was performed is an education and research hospital and the number of chronic patients who have been sick for a long time (duration of illness 12±7.32) and long-term drugs use present to this clinic. There were no individuals with MetS in the control group. This result shows the higher incidence of MetS among schizophrenic patients compared to the general Turkish public. Antipsychotics, especially multi-drug use, have been demonstrated in some studies as the cause for the development of MetS in schizophrenic patients (17). In this present study, no correlation was found between drug use and the

incidence of MetS. However, some studies have reported an increased incidence of insulin resistance and insulin levels in schizophrenic patients who have not used drugs (18).

In addition to the single carbon metabolism of vitamin B12 and its association with neuropsychiatric diseases, it is known to increase the risk of development of MetS in some groups (5,9,10). In their 2008 study, Yajnik et al. reported that insulin resistance increased in normal pregnant women with vitamin B12 deficiency (9). Adaikalakoteswari et al., in their 2015 study, reported that a vitamin B12 deficiency in healthy pregnant women and non-pregnant women cause an increased cholesterol and triglyceride synthesis and thus constitutes a risk factor for metabolic syndrome (10). Also Issac et al. in a 2015 study, demonstrated increased cholesterol levels and increased rates of memory loss as well as behavioral disorders in vitamin B12 deficiency in neuropsychiatric patients (19). In this study presented here, we observed a significant decrease in vitamin B12 and HDL levels in the schizophrenic patient group when compared to the control group. In addition, it was found that the vitamin B12 levels in 42% of the schizophrenic patients, who were diagnosed to have MetS, as being significantly lower compared to the schizophrenic patients without a diagnosis of MetS (p:0.012) and that the vitamin B12 levels in the schizophrenic patient group and systolic and diastolic blood pressures, TG, insulin, HOMA-IR and HbA1c values being significantly negatively correlated and significantly positively correlated with HDL levels suggest a possible role of vitamin B12 deficiency in the development of MetS in schizophrenic patients. No data were found in the literature about the role of vitamin B12 on the development of MetS in schizophrenic patient groups. One limitation of our study is the low number of patients.

The decreased vitamin B12 and serum BDNF levels in schizophrenic patients with a diagnosis of MetS compared to the other schizophrenic patients suggest that these two parameters might be associated with MetS. Although there are data published in the literature on the independent role of BDNF for Type 2 DM as well as antidiabetic or antilipidemic effects of BDNF, there is only one study evaluating the association of MetS and serum BDNF levels in schizophrenic patients (4,9,10). Thirty-one of 100 schizophrenic patients in that study had MetS. Serum BDNF levels were reported to be significantly lower in the group with MetS compared to the group without MetS and serum BDNF levels in schizophrenic patients were significantly negatively correlated to BMI, waist circumference, glucose, insulin and HOMA-IR and significantly positively correlated with HDL (2). These findings are compatible with our study and support the antidiabetic and antilipidemic effects of BDNF. In a 2015 study by Bonaccorso et al., BDNF Val66Met polymorphism was reported to increase BMI in 76 schizophrenic patients (20). In the experimental research of Teillon et al. published in 2010, BDNF was reported to have suppressing effects on PPAR-alpha and fibroblast growth factor 21 and lipid lowering effect and according to some studies, BDNF was considered possibly helpful in the treatment of diabetes (21). However Boyuk et al. in their 2014 study reported that BDNF was significantly increased in patients with Type 2 DM and thus BDNF was an important marker of Type2 DM (4). Although the diabetic and lipidemic effects of BDNF in patient groups other than schizophrenia have also been reported, we believe that the antidiabetic and antilipidemic effects of BDNF are at the forefront in schizophrenic patients as demonstrated in this present study. We also believe that the differences stem from ethnic and genetic differences.

Vitamin B12 and BDNF play a major role in the development of neurons (7). There are few studies evaluating the correlation of vitamin B12 and BDNF in the literature. BDNF expression was reported to be increased in the sciatic nerves of 96 rats that were administered vitamin B12, according to a study by Rathod et al. published in 2014 (22). In this study presented here, a significant positive correlation was found between vitamin B12 and BDNF in the patient and control groups. Especially in patients with MetS, compared to other schizophrenic patient group, vitamin B12 and BDNF were found to be significantly lower. These data suggest that deficiency in vitamin B12 and BDNF, which is correlated with this vitamin, might be the reason that MetS is seen in schizophrenic patients. Studies should be continued in larger patient groups to understand this issue in greater detail.

Several studies have been published evaluating MetS patients among schizophrenic patients. In those studies, patients with MetS were evaluated using PANSS and the psychopathological symptom severity was found to be higher. In a 2008 study by Arango et al. on 1,452 schizophrenic patients, the PANSS-total score of patients with MetS was reported to be higher (23). Also Fawzi et al., in their study performed in 100 schizophrenic patients in 2014, reported a significant positive correlation between PANSS-N, PANSS-P and PANSS-T to BMI, waist circumference, TC, TG, HDL and glucose (2). In our study, PANSS-N and PANSS-P were found to be positively correlated to waist circumference, glucose, TG, insulin, HOMA-IR and HbA1c. Also, the significantly increased PANSS-N and PANSS-P values in schizophrenic patients diagnosed with MetS, compared

to other schizophrenic patients, demonstrates that MetS negatively affects the psychopathological symptoms. To explore the reason for this, the correlation of PANSS and vitamin B12 and BDNF, which are known to be significantly low in patients with MetS, were evaluated. In our study, significant negative correlations were found between the PANSS-N, PANSS-P and PANSS-T syndrome scales and vitamin B12 and BDNF. This, in turn, demonstrates that psychopathological symptoms in schizophrenic patients with MetS are associated with vitamin B12 and BDNF. In a study published by Song et al. in 2014, no correlations were found between BDNF levels and PANSS-T, PANSS-N and PANSS-P, but significantly negative correlations were reported between folate levels and PANSS-T and PANSS-N syndrome scales (24). Yang et al., in their study on 129 schizophrenic patients published in 2011, reported that there was a significantly inverse correlation between PANSS-N subscale and BDNF (25). Misiak B. et al. (2014) in their study on 56 first episode schizophrenic patients, vitamin B12 and PANSS-Negative psychopathology score, and folate and PANSS general psychopathology score were found to be significantly and inversely correlated (8). In this present study however, a significantly inverse correlation was found between folate and PANSS-N syndrome scale. According to some studies, negative symptoms in schizophrenia were demonstrated to be derived from hypoactivity of dopaminergic system and BDNF was shown to have an important role in the differentiation and survival of dopaminergic neurons. These neurons were shown to include BDNF receptors. BDNF helps to decrease stress tension in schizophrenia and its deficiency exacerbates the psychopathological symptoms (26).

CONCLUSIONS

Schizophrenic patients should always be evaluated in terms of MetS development risk and vitamin B12 and folate levels should also be measured in addition to metabolic parameters. Psychopathological parameters in patients with MetS might be more severe compared to other patients with schizophrenia. Decreased levels of vitamin B12 and associated low levels of BDNF might be related to MetS development risk and increased psychotic symptoms. Also, the significant positive correlation of vitamin B12 and BDNF that was detected in this present study, points out that vitamin B12 deficiency might affect BDNF levels and thus MetS development might increase and psychotic symptoms might be exacerbated in schizophrenic patients. In addition, folate deficiency may also be correlated with the increase in the PANSS-negative syndrome scale, especially in schizophrenic patients.

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