

Total white blood cell count, liver enzymes, and metabolic syndrome in schizophrenia

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Background/aim: Metabolic syndrome (MetS) is an important clinical issue in patients with schizophrenia, but its associated factors are still ambiguous. The aim of the present study was to test whether there are any associations between MetS and white blood cell (WBC) levels, liver enzymes, or sociodemographic variables.

Materials and methods: The study included 91 patients with a diagnosis of schizophrenia. We used the National Cholesterol Education Program's Third Adult Treatment Protocol criteria to evaluate MetS in patients. Schizophrenia patients with MetS were compared with those without MetS on the basis of demographic and clinical characteristics and total WBC counts. We conducted Spearman's correlation and binary logistic regression analyses to achieve the best prediction of MetS in schizophrenia.

Results: Compared with schizophrenia patients without MetS, those with MetS were older, less educated, and more likely to be smokers. They were also more likely to have a longer duration of the illness, a longer untreated period, and higher alanine aminotransferase (ALT) and WBC levels. MetS was correlated with age, duration of illness, income, ALT, gamma-glutamyl transpeptidase, WBC, and hemoglobin values. Age and WBC levels were found to be the best predictors of MetS.

Conclusion: Hemograms and liver tests should be conducted to test for MetS in schizophrenia.

Key words: Schizophrenia, metabolic syndrome, white blood cells, alanine aminotransferase

1. Introduction

The prevalence of metabolic syndrome (MetS) is higher in people with schizophrenia than it is in the general population (1). The rate of MetS, according to the National Cholesterol Education Program's Third Adult Treatment Protocol (NCEP ATP III) criteria, was 40.9% in patients who participated in the Clinical Antipsychotic Trials of Intervention Effectiveness study (2). While there have been many studies measuring the prevalence rates of MetS in schizophrenia, there is limited information on the factors related to MetS in schizophrenic patients.

Among the factors that increase the risk of MetS are the use of antipsychotics, hyperphagia, diet-related weight gain, smoking, low levels of physical activity, difficulties dealing with stress, blood circulation abnormalities, changing physiology of fat cells, sex hormone abnormalities, changes in pituitary adrenal functioning, some genetic polymorphisms, and inflammation (3,4). Studies investigating the relationship between sociodemographic and clinical variables such as

education level, employment, economic status, marriage, age of illness onset, duration of illness, and number of hospitalizations have had conflicting results (4,5). Only age is consistently positively correlated with the rate of MetS in patients with schizophrenia (6).

Research on the biological correlates of MetS in schizophrenia must be improved. Hematologic parameters such as the total white blood cell (WBC) count are among these biological correlates. Recently, Na et al. (7) have argued that a higher WBC count shows a low-grade chronic inflammatory process in these particular patients. In the literature, there are only a limited number of studies investigating the WBC count as a risk factor for MetS in patients with schizophrenia (7-9). Similarly, there are few studies that investigated whether liver functions can predict MetS in schizophrenia patients (10).

In the present study, we looked at MetS related factors (demographic and clinical factors, along with total WBC count and liver and thyroid function tests) in patients with schizophrenia who were already undergoing treatment.

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2. Materials and methods

2.1. Participants

All participants were referred from the inpatient and outpatient psychiatry clinic at Yıldırım Beyazıt Training and Research Hospital. A total of 109 patients, diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), were enrolled in the present study. We excluded from the study 18 patients who did not consent to laboratory tests. All participants and their families received information about the study and signed the consent form, giving their informed consent. The study was approved by the Institutional Ethical Committee.

Patients between the ages of 18 and 25 and diagnosed with schizophrenia according to the DSM-IV were included in the study. Patients diagnosed with any psychiatric disorder other than schizophrenia, patients diagnosed with any type of metabolic disease (e.g., hypertension, diabetes mellitus, and hyperlipidemia), patients using oral contraceptives, or patients who were pregnant or breast feeding were excluded from the study.

2.2. Procedure

All participants underwent a Structured Clinical Interview for DSM-IV Axis I Disorders to confirm the diagnosis and exclude other psychiatric diagnoses (11,12). As part of the metabolic parameter analysis, the patients' biochemical and hematological measurements were determined using venous blood that was collected in the morning after a 12-h fasting period. The height, weight, blood pressure, and waist circumference of the patients were measured at the same time. The height and weight were measured with an electronic measurement device while the patients were fasting. Blood pressure was measured on the left arm after patients had rested for 5 min and while seated. We measured the waist circumference above the highest point of the iliac bone and at low respiration while patients were standing.

Medical histories, including treatment history, were taken from the patients and their relatives (and/or those who had lived with the patient and had information about their history with the disease). We also inspected hospital records.

Evaluations were carried out according to the 2001 NCEP ATP III criteria (13). According to these criteria, patients were evaluated with regards to obesity (defined as a waist circumference > 102 cm for men, and >88 cm for women), triglyceride levels (>150 mg/dL was considered hypertriglyceridemia), high density lipoprotein levels (\leq 40 mg/dL for men, and \leq 50 mg/dL for women), blood pressure (\geq 130/85 mmHg), and fasting blood glucose levels (\geq 100 mg/dL). A positive score in 4 of the 5 factors was accepted as a MetS diagnosis. The patients were then divided into 2 groups according to these results: schizophrenia patients with MetS and schizophrenia patients without MetS.

2.3. Statistics

We analyzed the data using SPSS 17 (Chicago, IL, USA). We used the Student's t-test, chi-square tests, ANOVA, and Spearman's correlation and stepwise regression analyses. $P < 0.05$ was considered significant.

3. Results

3.1. Demographics

We analyzed 91 patients who met the study criteria and whose condition had remained stable over the 6 months preceding the study. The demographics of the patient groups are provided in Table 1. We found that 32.5% of all patients had MetS. Table 1 shows that patients with MetS were older than schizophrenia patients without MetS, and the mean education level was lower in schizophrenia patients with MetS than in those without MetS.

Smoking rates and duration of smoking were significantly higher in schizophrenia patients with MetS than in patients without MetS ($t = 3.912$, $P = 0.048$ and $t = 3.222$, $P = 0.002$, respectively).

3.2. Clinical data

We found that, in the schizophrenia patients, the total treatment period was an average of 31.9 months, the final regular medication period was 12.7 months, and the total disease period was an average of 114.1 months. The total duration of psychosis was found to be 160.3 months in the patients with MetS, and 89.1 months in the patients without MetS. The duration of illness and untreated psychosis was found to be longer in patients with MetS.

The 3 types of treatments applied to patients with schizophrenia are atypical (69.2%), typical (6.6%), and combined antipsychotics (24.2%). The medicines that were most commonly used in treatment were olanzapine (36.3%, $n = 33$), risperidone (31.9%, $n = 29$), and clozapine (8.8%, $n = 8$). A daily dose of 525.2 mg of chlorpromazine was found to be the average equivalent dose of the last medication.

We did not find a significant relationship between the two groups in terms of the type of antipsychotic. Likewise, there was no difference between the chlorpromazine-equivalent doses of the last medicine and the duration of the medications between the groups ($P > 0.05$).

3.3. Laboratory data

Although 19.2% of patients in the study reported a medical disease, only 12.1% of these patients were taking medicine to treat their diseases. When the laboratory results were examined, we found that the following values were higher than normal: hemoglobin in 30.8% of patients, total cholesterol in 5.5%, fasting blood glucose in 8.8%, triglycerides in 19.8%, aspartate aminotransferase (AST) in 4.4%, alanine aminotransferase (ALT) in 14.3%,

Table 1. Comparison of demographic characteristics between the two groups.

		Schizophrenia with MetS* Schizophrenia without MetS					
		Mean ± SD†		Mean ± SD		P	t / χ^2
Age		43.0 ± 10.6		31.7 ± 8.6		< 0.001	-5.519
Education (year)		7.4 ± 3.6		9.01 ± 3.4		0.035	2.137
Latest drug-free period (month)		2.80 ± 5.4		6.56 ± 10.6		0.030	2.186
Duration of total treatment (month)		15.57 ± 20.8		11.22 ± 20.5		0.340	-0.960
Duration of illness (month)		160.3 ± 87.5		89.1 ± 76.3		< 0.001 †	-4.037
		n (%)		n (%)			
Sex	Male	19	(37.3)	32	(62.7)	0.637	0.222
	Female	13	(32.5)	27	(67.5)		
Regular work	Regular job	17	(53.1)	43	(72.9)	0.058	3.605
	Unemployed	6	(18.8)	12	(20.3)		
	Retirement	9	(28.1)	4	(6.8)		
Income	Low	2	(6.3)	8	(13.6)	0.287	1.133
	Middle/High	30	(93.8)	51	(86.4)		
Alcohol use	No	30	(93.8)	53	(89.8)	0.528	0.397
	Yes	2	(6.3)	6	(10.2)		
Smoking	No	6	(18.8)	23	(39)	0.048	3.912
	Yes	26	(81.3)	36	(61)		
Comorbid medical disease	No	25	(78.1)	48	(81.4)	0.712	0.136
	Yes	7	(21.9)	11	(18.6)		
A family history of medical illness	Yes	11	(34.4)	13	(22)	0.202	1.627
	No	21	(65.6)	46	(78)		

*MetS: metabolic syndrome.

SD†: standard deviation.

Bolded values are significant.

gamma-glutamyl transpeptidase (GGT) in 8.8%, and thyroid-stimulating hormone (TSH) in 6.6%. In terms of medical comorbidities, there was no difference between schizophrenia patients with MetS and those without MetS.

A comparison of laboratory parameters between the groups is shown in Table 2, where parameters of MetS are represented along with thyroid function tests. All liver enzymes were higher in the MetS group, but the difference was significant only for the ALT ($P = 0.008$, $t = -2.337$) values. In addition, the leukocyte count was higher ($P < 0.01$, $t = -3.049$) in patients with MetS.

3.4. Correlation analysis and binary regression analysis

MetS was correlated with age ($r = 0.510$, $P < 0.001$), duration of illness ($r = 0.372$, $P < 0.001$), duration of smoking ($r = 0.387$, $P = 0.002$), income ($r = 0.237$, $P = 0.024$), ALT ($r = 0.257$, $P < 0.016$), GGT ($r = 0.417$, $P < 0.001$), WBC ($r = 0.344$, $P = 0.001$), and hemoglobin levels ($r = 0.279$, $P = 0.009$).

Binary regression analysis (backward conditional) was conducted to construct a model for the best prediction of MetS. Only significantly correlated factors underwent regression analysis. The model was found to be significant ($P = 0.012$), and the fitting of the model was acceptable ($r = 0.501$). It represents a 73.9% specificity rate, a 90.9% sensitivity rate, and an 85.1% total rate for the prediction of MetS. The model of the regression analysis excluded the following variables: GGT, ALT, hemoglobin, duration of illness, and income. Age ($B = 0.062$, standard error = 0.013, Beta = 0.447, $t = 4.704$, $P < 0.001$) and WBCs ($B = 0.167$, standard error = 0.060, Beta = 0.282, $t = 2.784$, $P = 0.007$) were found to be predictors of MetS.

4. Discussion

In the general population the prevalence of MetS varies from country to country. For example, in the United States the frequency of MetS is 25%–34% in the general

Table 2. Comparison of laboratory parameters between the two groups.

	Schizophrenia with MetS*	Schizophrenia without MetS	P	t
	Mean ± SD†	Mean ± SD		
Weight (kg)	88.4 ± 12.9	66.8 ± 11.6	<0.001	-8.106
Systolic blood pressure (mmHg)	121.2 ± 16.9	111.0 ± 12.2	0.004	-3.008
Diastolic blood pressure (mmHg)	78.5 ± 10.4	73.3 ± 8.2	0.019	-2.611
Waist circumference (cm)	107.5 ± 9.7	85.8 ± 11.5	<0.001	-8.987
Triglycerides (mg/dL)	281.6 ± 113	126.1 ± 64.0	<0.001	-8.204
High-density lipoprotein (mg/dL)	32.9 ± 6.5	47.2 ± 11.0	<0.001	6.365
Fasting blood glucose (mg/dL)	103.6 ± 17.5	90.58 ± 13	0.001	-3.642
BMI (kg/m ²)	32.0 ± 8.5	24.0 ± 7.4	<0.001	-7.401
TSH	1.5 ± 1.2	1.5 ± 0.9	0.805	0.248
T3	3.3 ± 0.8	3.4 ± 1.2	0.763	-0.304
T4	1.4 ± 0.5	1.4 ± 0.2	0.883	0.147
AST	21.4 ± 9.2	20.8 ± 8.0	0.585	0.270
ALT	27.2 ± 17.6	18.9 ± 12.0	0.008	-2.337
GGT	44.5 ± 4.4	30.9 ± 6.3	0.858	-1.049
ALP	178.4 ± 90.3	155.1 ± 53.7	0.247	-1.117
LDH	246.5 ± 125.4	220.1 ± 73.9	0.290	-0.914
Hemoglobin (g/dL)	14.3 ± 02.0	14.0 ± 63.5	0.73	-0.338
Leukocyte (K/uL)	8.72 ± 2.6	7.14 ± 1.7	<0.001	-3.049
Platelet (K/uL)	275.7 ± 90.2	257.7 ± 55.8	0.25	-1.157

*MetS: metabolic syndrome.

SD†: standard deviation.

Bolded values are significant.

population above the age of 20, and it is 23%–24% in Europe for the same age group (14,15). A recent systematic review reported that 32.5% of individuals with schizophrenia also have MetS (6). In the Turkish Adult Risk Factor Study conducted in 2000, the frequency of MetS was 28% in men and 45% in women (16). In other studies, the prevalence of MetS was found to range from 17.9% to 41.4% (17–19). We see that MetS prevalence is higher in Turkey than it is in Europe or in the United States. In our study, the MetS rate was found to be 35.2% among patients with schizophrenia. This result is in accordance with the elevated presence of MetS in the general Turkish population. A similar interpretation was presented in one of the largest studies from Turkey, which reported comparable results (20).

Schizophrenia patients with MetS were older than those without MetS. Similarly, schizophrenia patients with MetS had longer illness duration than those without MetS. This could be coincidental, making it difficult to determine whether age or length of disease is the main factor affecting MetS. Both of these factors were found to correlate with MetS in the Spearman's correlation analysis, but duration of illness had a weaker correlation ($r = 0.372$)

than age ($r = 0.510$). Regression analysis supported only age as a predictive factor. This finding is comparable with the results of a recent metaanalysis (6).

One of the most interesting findings of the present study was the relationship between WBC count and MetS. WBC count was significantly higher in schizophrenia patients with MetS than in those without MetS. WBC count was mildly correlated with MetS in the correlation analysis, while in the regression analysis it was one of the predictors of MetS. Three previous studies reported that a higher WBC count was associated with MetS (7–9). One of these studies determined that changes in WBC count were positively correlated with changes in waist circumference during a 24-week antipsychotic treatment period (7). In addition, total WBC count predicted the future development of MetS in the general population (9). The WBCs are known to be a mediator of inflammation. What is the specific meaning of this observed relationship for subjects with schizophrenia? Inflammatory processes are blamed for the etiology of not only MetS, but also of schizophrenia. The coincidence of these two conditions seems to be high. Patients with schizophrenia may have a predisposition

to develop MetS independent of antipsychotic use (21). Inflammation could be causatively connected to both MetS and schizophrenia. These inflammatory processes may originate from genetic factors, environmental factors, or a combination of both.

The other original finding of the present study is the association between ALT and MetS in subjects with schizophrenia. ALT is a marker sensitive to nonalcoholic fatty liver disease, which is strongly connected to the existence of MetS (22). Recently, Kim et al. (10) reported that ALT levels were associated with the incidence of MetS in a longitudinal study of patients with schizophrenia. Ekstedt et al. (23) had similar results with nonalcoholic fatty liver disease patients. Lee et al. (24) published a study showing an association between the prevalence

of MetS and ALT. In this regard, ALT could provide a way to identify schizophrenic patients who are at risk of developing MetS and who need intensive attention.

The main limitations of the present study are the small sample size and the absence of healthy control groups.

Every patient with schizophrenia is a potential MetS patient, and thus the prevention of MetS is crucial. Follow-up with schizophrenia patients must be structured not only for psychiatric clinical parameters, but also for medical clinical parameters. Some routine laboratory examinations, like total WBC and ALT tests, may help to determine in advance the manifestation of MetS. These findings may also enhance the understanding of the underlying mechanisms of MetS in schizophrenia patients.

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