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Article

Correlation of Hematologic Coefficients of Inflammation and Metabolic Syndrome: Pilot Study

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Abstract: Antipsychotic therapy often causes side effects, one of which is metabolic syndrome. This condition increases the risk of cardiovascular disease and increases mortality in patients with schizophrenia. Currently, to improve the safety of antipsychotic therapy, the possibility of introducing into clinical practice the monitoring of hematologic inflammation coefficients as predictors of the development of metabolic syndrome is being considered. **Objective:** was to determine the presence of correlation between hematologic inflammation coefficients and metabolic syndrome in patients with schizophrenia. **Methods:** The study included 32 patients diagnosed with schizophrenia paranoid (F20.0, ICD-10), treated in a psychiatric hospital and receiving clozapine therapy. Patients were divided into two groups according to the presence or absence of metabolic syndrome. Metabolic syndrome was defined according to the International Diabetes Federation criteria. The groups were matched as similar as possible in terms of sex, age, therapy, smoking status and comorbidities of the patients. **Results:** In our study, no significant differences were found between patients with absence and presence of metabolic syndrome in terms of hematologic inflammation coefficients: neutrophil to lymphocyte ratio (p=0.752), monocyte to lymphocyte ratio ($p = 0.734$), systemic immune inflammation index (SII) (p=0.564), monocyte to high density lipoprotein ratio ($p = 0.169$). **Discussion.** The results of our study showed no significant differences between schizophrenic patients with metabolic syndrome and those without metabolic syndrome in terms of hematologic inflammatory coefficients. This may suggest that these inflammatory markers are not reliable predictors of the development of metabolic syndrome in patients with schizophrenia receiving clozapine therapy. **Conclusion**. However, these findings require further investigation, as existing data on the relationship between inflammatory processes and metabolic disorders in patients with psychiatric disorders remain inconsistent.

Keywords: *hematologic inflammation coefficients; metabolic syndrome; schizophrenia.*

1. INTRODUCTION

Patients with schizophrenia have a lower life expectancy compared to the general population. They are more likely to develop cardiovascular, respiratory and metabolic disorders [1]. Cardiovascular disease is the leading cause of death in these patients [2]. Antipsychotic drugs play a key role in the treatment of schizophrenia by reducing relapse rates and have been used for decades. However, despite the emergence of new drugs, side effects remain a problem [3]. Experience shows that many of these effects can be prevented or minimized [4]. One of the serious side effects of antipsychotics is metabolic syndrome (MetS). As defined by the American Heart Association and the National Heart, Lung, and Blood Institute, MetS is a set of interrelated metabolic risk factors that increase the likelihood of atherosclerotic cardiovascular disease [5]. Risk factors such as diabetes, hypertension, and hyperlipidemia significantly increase the likelihood of cardiovascular disease in patients with MetS. These conditions contribute to the progression of atherosclerosis, increasing the risk of stroke, coronary heart disease and other

complications. Studying the association between inflammatory markers in the blood and MetS may help identify high-risk patients and take preventive measures. Studies support the association between hematologic parameters and MetS [6]. Inflammation is a complex process involving many biological mechanisms and is closely related to oxidative stress [7]. Markers of systemic inflammation determined by clinical blood analysis reflect the level of oxidative stress in patients with schizophrenia [8].

Recently, hematologic inflammation coefficients (HICs) include neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), monocyte to high-density lipoprotein ratio (MHR), and systemic immune inflammation index (SII), which calculated by the formula SII (platelet count * neutrophil/lymphocyte count) [9]. HICs have been proposed as markers of inflammation. Studies have shown a significant correlation of HICs on the basis of blood clinical analysis with other established markers of inflammation (CRP, indicators of oxidative stress and some pro-inflammatory cytokines) [10]. It is important to note that studies have shown that HICs is not affected by modifying factors, which shows its advantage over other commonly used inflammatory markers [11]. These indicators are easy to define, inexpensive and correlate with cardiovascular risk and mortality [12].

The aim of this pilot study is to determine the existence of a relationship between HICs and MetS in patients with schizophrenia.

2. MATERIALS AND METHODS

The study was conducted on the basis of the Institute of Personalized Psychiatry and Neurology (IPPN) of V.M. Bekhterev National Medical Research Center for Psychiatry and Narcology of the Ministry of Health of the Russian Federation in January 2025. The study included 32 patients with an established diagnosis of schizophrenia paranoid, treated in a psychiatric hospital during stabilizing therapy with clozapine. The diagnosis of schizophrenia paranoid was established in accordance with the diagnostic criteria F20.0 of the International Classification of Diseases 10th revision [13].

Patients were divided into two groups of 16 people: group 1 (patients without MetS); group 2 (patients with MetS). MetS was defined according to the International Diabetes Federation criteria: presence of central obesity (body mass index (BMI) > 30 kg/m^2), high density lipoprotein (HDL) level < 1.03 mmol/L (men) or < 1.29 mmol/L (women), fasting glucose level ≥ 5.6 mmol/L [5]. The groups were selected to be as similar as possible in terms of sex, age, smoking status, therapy, and absence of serious acute and chronic diseases that could affect the results of the study [14, 15].

Statistical processing of the data was performed using the free software Jamovi (Version 2.3). The distribution was evaluated using the Shapiro-Wilk criterion. Central tendencies were presented as arithmetic mean, standard deviation, median and interquartile ranges as M ± SD (Me; Q_1; Q_3). Categorical and rank variables were presented as number of cases - absolute number (n) and proportion - relative number (%). To assess intergroup differences in unrelated samples based on the nature of the sampling distribution, parametric t-Student test or non-parametric U-Mann-Whitney test were used. χ^2-Pearson test was used to assess the association of nominal variables. The significance of the models was evaluated based on F-Fisher and rho-Spearman criteria. The critical significance level p at which the null hypothesis was rejected was *p*-value = *0.05*.

The study was approved by the Local Ethical Committee: (protocol No. 9 of December 21, 2023) and complied with the Ethical Standards of the World Medical

Association Declaration of Helsinki. All patients signed informed voluntary consent to participate in the study.

3. RESULTS

Each study group included 9 men and 7 women, of whom 6 were smokers and 10 non-smokers. No statistically significant differences were found when comparing the clinical and demographic parameters of the two groups. The age of patients in the first group was 50.7±9.46 years (Me 53.0; Q_1 = 49.0; Q_3 = 58.3), in the second group - 50.6 ± 9.28 years (Me 53.0; Q_1 = 48.3; Q_3 = 58.3).

Clinical characteristics of the two groups according to the criteria of MetS (Table 1): BMI (*p*-value < *0.001*), fasting blood glucose level (*p*- value < *0.001*), HDL (*p*- value = *0.05*). Patients with MetS took a lower dose of clozapine than patients without metabolic syndrome.

In our study, there were no significant differences between groups in HICs: NLR (*p*- value = *0.752*), MLR (*p*- value = *0.734*), SII (*p*- value = *0.564*), and MHR (*p*- value = *0.169*) (Table 2).

Table 1. Criteria of metabolic syndrome in schizophrenic patients with (group 1) and without (group 2) clozapine-induced metabolic syndrome

Criteria	Group	Patient number	Mean	Median	SD	SE
BMI	1	16	23.5	22.4	3.15	0.788
	2	16	33.7	32.8	4.37	1.09
Glucose	1	16	4.73	4.71	0.480	0.120
	2	16	6.26	5.90	1.20	0.300
HDL	1	16	1.20	1.18	0.347	0.0868
	2	16	0.954	0.950	0.179	0.0449
Clozapine dose	1	16	225	200	146	36.4
	2	16	157	150	86.1	21.5

Note: *1 - patients without MetS, 2 - patients with MetS, BMI - body mass index, Glucose - fasting blood glucose level, HDL - high-density lipoproteins, SD - standard deviation, SE - standard error of the mean.*

Table 2. Hematological inflammation coefficients in in schizophrenic patients with (group 1) and without (group 2) clozapine-induced metabolic syndrome

Criteria	Group	Patient number	Average		Median	SD	SE	*p-value*
NLR	1	16	2.92		2.02	2.76	0.689	*0.752*
	2	16	2.30		2.09	0.967	0.242	
MLR	1	16	0.304		0.265	0.135	0.0337	*0.734*
	2	16	0.336		0.280	0.182	0.0456	
SII	1	16	632		596	490	123	*0.564*
	2	16	617		620	290	72.5	
MHR	1	16	0.506		0.515	0.179	0.0448	*0.169*
	2	16	0.625		0.673	0.239	0.0597	

***Note*:** *1 - patients without MetS, 2 - patients with Mets, NLR - neutrophil to lymphocyte ratio, MLR - monocyte to lymphocyte ratio, MHR - monocyte to high-density lipoprotein ratio, SII - systemic immune inflammation index, SD - standard deviation, SE - standard error of the mean.*

4. DISCUSSION

The results of our study showed no significant differences between schizophrenic patients with MetS and those without MetS in terms of HICs. This may suggest that these inflammatory markers are not reliable predictors of the development of MetS in patients with schizophrenia receiving clozapine therapy. However, these findings require further investigation, as existing data on the relationship between inflammatory processes and metabolic disorders in patients with psychiatric disorders remain inconsistent.

Systematic reviews to identify the relationship of NLR and MLR with the development of MetS in schizophrenic patients have not found sufficient information on this topic. The authors concluded that to date the role of HICs in the pathogenesis of psychiatric disorders, their participation in the mechanisms of development of comorbid conditions, including MetS, has not been sufficiently studied, there are only single publications [16, 17]. For example, in a published clinical case of a 48-year-old patient with schizophrenia, an increase in HICs was recorded against the background of treatment of symptom exacerbation after clozapine prescription, which preceded the development of MetS. The authors suggest a causal relationship between these processes and suggest a wider implementation of hematologic predictors of MetS in real clinical practice to improve the safety of antipsychotic therapy [18].

It can be assumed that the formulated research hypothesis has not yet been tested regarding the risk of MetS development depending on the indicators of systemic inflammation in patients with schizophrenia. Whereas clinical and biological associations have already been found for other psychiatric disorders, in particular bipolar disorder [19 - 22].

According to previous studies, antipsychotics themselves may cause inflammatory damage if their doses are too high for the person being treated [23], when taking clozapine, there was a tendency for the levels of systemic markers of inflammation to increase, with the exception of monocytes and MLR [24]. These results are consistent with experimental studies on animal models: an increase in neutrophils and a decrease in lymphocytes were observed several hours after a single injection of clozapine [25]. No correlation between the level of inflammatory markers and the daily dose of clozapine was found [24].

5. LIMITATION

The limitations of our study are the small sample of patients and the inclusion of only one antipsychotic in the analysis (clozapine). Despite these limitations, our study highlights the need to further investigate the role of hematologic inflammatory factors in the development of MetS in patients with schizophrenia. Future studies should include larger samples of patients receiving different antipsychotic medications and consider additional inflammatory biomarkers and metabolic parameters. This will allow to define more precisely the role of inflammatory processes in the pathogenesis of MetS and to develop strategies for its prevention and treatment in patients with schizophrenia.

6. CONCLUSION

The results of our study cannot confirm the relationship between HICs and MetS in patients with schizophrenia. The proposed study is novel and has both practical and theoretical significance, therefore, further study of the relationship between HICs and MetS in patients with schizophrenia should be continued.

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