The article is devoted to the 75th anniversary of Nikolai A. Kornetov, founder of integrative biomedical (clinical) anthropology, which combines the aspects of morphological and clinical sciences for a clearer understanding of development, clinical presentation, course, and outcomes of a disease

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Constitutional and morphological basis of the metabolic syndrome in patients with schizophrenia and persons without mental disorders

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ABSTRACT

Aim. To identify differences or comparability of constitutional-morphological characteristics and indicators of the fatty constitution between patients with schizophrenia and people with MetS and without mental disorders.

Materials and methods. We examined 63 patients with schizophrenia and MetS (25 women, 38 men), aged 30 [33;52], and 50 mentally healthy individuals with MetS (28 women, 22 men) aged 57 [49; 60]. The main criterion for inclusion in the study was the presence of a verified MetS according to the criteria of the International Diabetes Federation. Anthropometric examination was performed according to the method of V.V. Bunak (1941) with the underlying calculation of integral indices. The determination of the fat component included: measuring waist circumference; non-invasive bioimpedancemetry – body weight, BMI, total and visceral fat content; determination of the total fat fold (electronic caliper). In the blood serum, the concentration of glucose, total cholesterol, HDL, TG was determined using standard commercial kits, the calculation of LDL and the Atherogenic Index.

Results. Differences in the prevalence of the constitutional-morphological type and the type of somatic sexual differentiation were not established in the groups. The level of visceral fat and BMI were higher in mentally healthy individuals with MetS than in schizophrenic patients with MetS ($p = 0.005$ and $p = 0.0001$, respectively). Patients with schizophrenia and MetS had low serum glucose levels compared with individuals without mental disorders ($p = 0.0001$). An increase in the level of TG and the Atherogenic Index was found in patients with schizophrenia with MetS ($p = 0.026$ and $p = 0.03$, respectively), and the level of HDL was reduced ($p = 0.022$).

Conclusion. The constitutional and morphological basis of MetS in patients with schizophrenia and persons without mental disorders is the same, however, changes in the fat constitution were determined for mentally healthy individuals. Changes in the lipid profile and glucose concentration may be associated with the presence of MetS-specific risk factors for patients with schizophrenia.

Keywords: schizophrenia, metabolic syndrome, constitution, BMI, visceral obesity, lipid spectrum.

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Конституционально-морфологические основы метаболического синдрома у пациентов с шизофренией и лиц без психических расстройств

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РЕЗЮМЕ

Цель: выявить различия или сопоставимость конституционально-морфологических характеристик и показателей жировой конституции между пациентами с шизофренией и лицами с метаболическим синдромом (МС) без психических расстройств.

Материалы и методы. Обследованы 63 пациента с шизофренией и МС (25 женщин, 38 мужчин) в возрасте 30 [33; 52] лет и 50 психически здоровых лиц с МС (28 женщин, 22 мужчины) в возрасте 57 [49; 60] лет. Основным критерием включения в исследование являлось наличие верифицированного МС по критериям Международной федерации диабета (IDF). Антропометрическое обследование выполнено по методике В.В. Бунака (1941) с последующим вычислением интегральных индексов. Измерение жировой компоненты включало: проведение измерения окружности талии; неинвазивную биоимпедансометрию – масса тела, индекс массы тела (ИМТ), содержание общего и висцерального жира; определение суммарной жировой складки (электронный калипер). В сыворотке крови определена концентрация глюкозы, общего холестерина, холестерина липопротеидов высокой плотности (ХС-ЛПВП), триглицеридов (ТГ) с использованием стандартных коммерческих наборов, расчет показателей ХС-ЛПНП и индекса атерогенности.

Результаты. Различия в частоте встречаемости конституционально-морфологического типа и типа соматической половой дифференциации не были установлены в группах сравнения. Уровень висцерального жира и ИМТ были значительно выше у психически здоровых лиц с МС, чем больных шизофренией с МС ($p = 0{,}005$ и $p = 0{,}0001$ соответственно). Пациенты с шизофренией и МС имели низкий уровень концентрации глюкозы в сыворотке крови по сравнению с лицами без психических расстройств ($p = 0{,}0001$). Обнаружено повышение уровня ТГ и индекса атерогенности у больных шизофренией с МС ($p = 0{,}026$ и $p = 0{,}03$ соответственно), а уровень ХС-ЛПВП был снижен ($p = 0{,}022$).

Заключение. Конституционально-морфологическая основа формирования МС у больных шизофренией и лиц без психических расстройств является одинаковой, однако изменения в жировой конституции были определены для психически здоровых лиц. Изменения в липидном профиле и концентрации глюкозы могут быть связаны с наличием специфичных для больных шизофренией факторов риска МС.

Ключевые слова: шизофрения, метаболический синдром, конституция, ИМТ, висцеральное ожирение, липидный спектр

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом НИИ психического здоровья Томского НИМЦ (протокол № 99 от 17.04.2017).

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INTRODUCTION

The development of metabolic syndrome (MetS) increases the risk of developing cardiovascular diseases, insulin resistance, diabetes mellitus, as well as vascular and neurological complications [1]. MetS is associated with the risk of death for mentally healthy individuals [2], for patients with schizophrenia, it is increased by almost 2–4 times [3].

Antipsychotic therapy is a factor for the development of MetS in patients with schizophrenia and an increase in the deterioration of the metabolic profile in the first two years of therapy, especially for younger patients and for individuals with the first episode [4]. Although various criteria for diagnosing MetS are used, the prevalence of MetS increases over time in the age group from 20 to 29 years: according to ATP III A criteria the increase is from 38.9 to 53.0% and according to IDF, it is from 43.6 to 55.7% [5].

Treatment with conventional or atypical antipsychotics is associated to varying degrees with the incidence of metabolic disorders. In this series, quetiapine, olanzapine, and clozapinum can be distinguished as antipsychotics with the highest risk of developing MetS, while aripiprazole and haloperidol have a low risk [6].

Individual components of the fat constitution, namely, an increase in waist circumference parameters and body mass index (BMI), are associated with the risk of developing MetS in patients with schizophrenia [7]. Also, an increase in subcutaneous and visceral fat was found during treatment with antipsychotics, while the total body fat percentage did not increase in patients with schizophrenia compared with healthy controls [8].

Previously, constitution as a structural biomarker was found to have a crucial role in the development of visceral obesity in patients with schizophrenia while they were treated with antipsychotics [9]. The asthenic constitutional and morphological type was identified as a risk factor for the development of MetS in patients receiving risperidone, and the type of somatic sexual differentiation was identified for quetiapine. This was an extended application of the anthropological method in psychiatry, which was traditionally used in relation to the clinical presentation and the course of mental disorders [10] to assess a response to therapy and its safety. Some studies also demonstrated the association of anthropometric parameters including an increase in BMI and waist-to-hip ratio with the risk of sudden cardiac death, which was explained by the development of metabolic disorders in mentally healthy population [11].

The study of the relationship between epicardial fat, obesity, visceral fat, and MetS components showed the contribution of the components to the risk of developing coronary heart disease [12]. Schizophrenia patients were found to have a higher incidence of abdominal obesity, hypertriglyceridemia, and a decrease in the level of high-density lipoproteins, while there was a slight decrease in the incidence of hyperglycemia when compared with mentally healthy individuals [13]. The predictive value of high-density lipoprotein cholesterol (HDL-C) in relation to MetS was recognized as the highest in patients with schizophrenia receiving antipsychotic therapy [14]. It should be noted that MetS has a complex and systemic pathogenesis, however, along with other possible predictors, sedentary lifestyle and unbalanced diet play a fundamental role in its development [15].

Studies demonstrate the contribution of individual anthropometric indicators to the development of MetS in both patients with schizophrenia and individuals without mental disorders. Previously, no studies were conducted aimed at comparing constitutional factors in the formation of MetS between these two groups.

The aim of the study was to identify differences or comparability of constitutional and morphological characteristics and indicators of the fat constitution between patients with schizophrenia and people with MetS without mental disorders.

MATERIALS AND METHODS

The study was carried out in the clinics of the Mental Health Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences (second clinical department) and Siberian State Medical University (endocrinology department). All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Mental Health Research Institute of Tomsk NRMC (Protocol No. 99 of 17.04.2017).

Two study groups were formed: patients with schizophrenia and mentally healthy individuals with MetS. The main criterion for inclusion in the study was the presence of a verified MetS diagnosis according to the criteria of the International Diabetes Federation (IDF) (2005) [16], which include the presence of abdominal obesity (waist circumference ≥ 94 cm in men and ≥ 80 cm in women) accompanied by 2 or more of the following factors: an increase in triglycerides ≥ 1.7 mmol / l or receiving specific treatment for this dyslipidemia; cholesterol ≤ 1.03 mmol / l in men and 1.29 mmol / l in women; a decrease in HDL or receiving specific treatment for this dyslipidemia; increased blood pressure ≥ 130 / 85 mm Hg or receiving antihypertensive therapy; an increase in fasting blood glucose ≥ 5.6 mmol / l or the previous diagnosis of type 2 diabetes mellitus. Criteria for inclusion in the study were as follows: the age of patients from 18 to 60 years, a verified diagnosis of schizophrenia according to the criteria for studies according to ICD-10 [17] (for patients from a psychiatric hospital), belonging to the Caucasian race, and an ability to give a written informed consent. Exclusion criteria were the presence of organic, neurological, and severe somatic disorders leading to organ failure, and refusal to participate in the study. All patients with schizophrenia at the time of inclusion in the study received basic antipsychotic therapy at therapeutic doses approved by the Ministry of Healthcare of the Russian Federation.

An anthropometric examination was performed according to the method of V.V. Bunak (1941) [18], adopted at the Research Institute and the Museum of Anthropology named after D.N. Anuchin of Lomonosov Moscow State University. The determination of constitutional and morphological types and somatic sexual differentiation was carried out using the calculation of the Rees-Eysenck Body Index [19] and the Tanner scale [20].

The measurement of the fat component included measuring waist circumference (measuring tape); non-invasive bioimpedancemetry (medical device "Omron BF508", Japan) – body weight, BMI, total and visceral fat; total fat fold (electronic caliper) which consisted of the sum of the fat fold values of the shoulder, back, abdomen, and lower leg.

Blood sampling was carried out after a 12-hour overnight fasting by antecubital venipuncture into clot activator tubes (CAT; BD Vacutainer). To isolate serum samples, the tubes were centrifuged for 30 min at 2,000 g at 4 °C. Serum was stored at –20 °C (or –80 °C) before the analysis. The concentration of total cholesterol (TC), HDL, triglycerides (TG), and glucose in blood serum was determined by the enzymatic colorimetric method using standard commercial kits (Cormay, Poland). Low-density lipoprotein (LDL) concentrations were calculated using the Friedewald equation (1972) [21]. The atherogenic index was calculated according to the formula proposed by A.N. Klimov (1977) [22].

The obtained data were tested for normal distribution using the Kolmogorov – Smirnov test (with the Lilliefors correction) and the Shapiro – Wilk test. Quantitative data were presented as the median and the interquartile range Me [Q_1; Q_3]. Qualitative data were presented by frequency indicators (n (%)). A statistical analysis was performed using the Statistica software for Windows 12.0. Pearson's $\chi 2$ test was used to compare the frequencies. The Mann – Whitney U-test was used to compare two independent samples of quantitative data. The threshold value of the achieved significance level was $p \leq 0.05$.

RESULTS

We examined 63 schizophrenia patients with MetS (25 women, 38 men) aged 30 [33; 52] years and 50 mentally healthy individuals with MetS (28 women, 22 men) aged 57 [49; 60] years. The study groups were comparable by sex (p = 0.084), however, mentally healthy individuals with MetS were significantly older than schizophrenia patients (p = 0.0001).

The groups were compared according to the frequency of occurrence of the constitutional and morphological type. We did not establish statistically significant differences between patients with schizophrenia and mentally healthy individuals with MetS (Table 1). In both groups, persons with the andromorphic type prevailed – 65.1% and 56.0%, respectively.

Table 1

Constitutional and morphological types in the study groups

Indicators	Patients with schizophrenia and MetS		Mentally healthy individuals with MetS		*p*
	Abs.	%	Abs.	%	
Asthenic	7	11.1	0	0.0	–
Mesomorph	35	55.6	24	48.0	0.453
Hypersthenic	21	33.3	26	52.0	0.055
Total	63	100.0	50	100.0	–

In relation to the type of somatic sexual differentiation, differences were not established in both study groups ($p = 0.565$) and pairwise comparison (Table 2).

Table 2

Type of somatic sexual differentiation in the study groups

Indicators	Abs.	%	Abs.	%	*p*
Andromorphic	41	65.1	28	56.0	0.339
Mesomorph	9	30.2	18	36.0	0.549
Gynecomorphic	3	4.8	4	8.0	0.697
Total	63	100.0	50	100.0	–

Comparison of indicators of the fat component in body composition is presented in Table 3. It was found that BMI and visceral fat levels were significantly higher in mentally healthy individuals with MetS than in patients with schizophrenia and MetS ($p = 0.005$ and $p = 0.0001$, respectively). This may be due to their older age and, as a result, longer duration of obesity and the risk of developing insulin resistance and prediabetes.

Table 3

Indicators of the fat component in the body composition in patients with schizophrenia and mentally healthy people with metabolic syndrome, *Me* [Q_1; Q_3]

Indicators	Patients with schizophrenia and MetS	Mentally healthy individuals with MetS	*p*
Body weight, kg	95.0 [84.2; 105.7]	95.7 [89.1; 106.5]	0.164
Waist, cm	105.0 [96.5; 114.0]	109 [101; 115]	0.205
BMI	31.2 [27.5; 35.9]	33.7 [31.5; 38.3]	0.005
Total body fat	36.4 [30.5; 47.5]	40.8 [33.7; 48.4]	0.176
Visceral fat level	11 [9; 14]	13 [11; 17]	0.0001
Total fat fold	116 [86; 135]	121 [101; 143]	0.167

It was found that patients with schizophrenia and MetS had a low level of glucose in blood serum compared to mentally healthy individuals with MetS, which was statistically significant ($p = 0.0001$). The increase in lipid spectrum indicators for the level of TG and the atherogenic index was revealed in patients with schizophrenia and MetS ($p = 0.026$ and $p = 0.03$, respectively), and the level of HDL-C was reduced ($p = 0.022$) (Table 4).

Table 4

Glucose and lipid profile in patients with schizophrenia and mentally healthy people with metabolic syndrome, mmol / l, *Me* [Q_1; Q_3]

Indicators	Patients with schizophrenia and MetS	Mentally healthy individuals with MetS	*p*
Glucose	5.20 [4.70; 5.85]	5.70 [5.40; 6.40]	0.0001
TC	5.00 [4.04; 5.61]	4.66 [3.83; 5.62]	0.783
TG	2.00 [1.74; 2.41]	1.85 [1.50; 2.10]	0.026
HDL-C	0.90 [0.70; 1.10]	1.00 [0.90; 1.20]	0.022
LDL	2.92 [2.05; 3.72]	2.90 [2.10; 3.92]	0.804
Atherogenic index	4.26 [3.42; 5.98]	3.67 [2.67; 4.50]	0.030

DISCUSSION

The results obtained suggest that the constitutional and morphological basis for the formation of MetS in patients with schizophrenia and in mentally healthy individuals is the same. The results are of fundamental importance, since they confirm the general pathophysiology of MetS [23] in different groups of patients and the role of the bone component of the constitution as a time-stable structural marker in the mechanisms of MetS development. This indicates that the constitution affects the risk of developing MetS to a greater extent than antipsychotic drugs and schizophrenia itself as a pathological process accompanied by immune inflammation, even though their significant contribution to MetS is well known [24, 25].

However, differences were found in the fat constitution, since such indicators as BMI and visceral fat level increased in mentally healthy individuals with MetS compared with patients with schizophrenia and MetS. Previously, it was shown that the determination of BMI has a prognostic value for clinical screening of metabolic disorders in patients with schizophrenia, namely, persons whose BMI was 28 kg / m^2 and above had a higher risk of developing MetS than persons with an indicator below this threshold value [26].

Also, the literature provides evidence that for mentally healthy individuals, the level of BMI is not defined as a possible marker for the prognosis of metabolic disorders [27].

Currently, one of the key pathophysiological factors in the onset of MetS is an increase in the visceral fat [15], it is believed that this parameter can be a reliable predictor of the risk of developing metabolic disorders [28]. There is also an opposite point of view, where the study did not establish differences in the distribution of visceral fat in patients with schizophrenia receiving antipsychotic therapy and the control group according to magnetic resonance imaging (MRI) [29].

Changes in the metabolism of glucose and lipids in patients with schizophrenia are observed after 2 weeks and reach a maximum after 3 months while receiving antipsychotic therapy [30]. It was determined that fasting plasma glucose, insulin, and glucose in an oral glucose tolerance test increased and insulin resistance formed in patients with the first episode of schizophrenia, previously not treated with neuroleptics, compared with mentally healthy individuals, which may indicate the development of glucose metabolism disorders in patients before therapy [31].

In this study, individuals with schizophrenia and MetS had low serum glucose level. Glucose level increased in mentally healthy individuals with MetS, which is consistent with an increase in indicators such as BMI and visceral fat level in this group. Impaired glucose metabolism reflects the formation of insulin resistance, which leads to the development of visceral obesity, dyslipidemia, and its progression [32].

In the first 6 months of antipsychotic therapy in patients with schizophrenia, a correlation was found between the development of metabolic disorders in the form of dyslipidemia with low HDL levels and an increase in waist circumference [33]. The effect of a pharmacological agent on neurohumoral systems, namely the metabolism of leptin, adiponectin, ghrelin, orexin and cholecystokinin, dopaminergic, serotonergic, adrenergic, and histamine receptors, which are considered to be biomarkers of metabolic disorders, is associated with the formation of MetS [34], an increase in TC, TG, and LDL-C, and a decrease in HDL-C in patients with schizophrenia [35].

The revealed differences in the age of patients in the comparison groups can be explained by the fact that patients were included in the study at the same time, which was determined by the design of the study. It can be assumed that the older age of inpatients with MetS reflects the general picture of MetS development in the general population, where the overall prevalence of MetS increases with age: 15–39 years – 13.9%; 40–59 years – 26.4%, > 60 years – 32.4% [36]. Previously, gender and age differences were also shown for patients with schizophrenia, namely, women with MetS were older, had longer duration of MetS, and developed it later than men with MetS [37].

The new results obtained in this study are considered from interdisciplinary perspective, which is widely used to assess mental health [38]. In this case, the application of the anthropological approach in psychoendocrinology made it possible to find clinical and biological similarities and differences in the characteristics of MetS in patients with schizophrenia and individuals without mental disorders.

CONCLUSION

The comparative analysis of constitutional and morphological characteristics in the groups of patients with schizophrenia and MetS and mentally healthy individuals with MetS did not show significant differences in the constitutional and morphological type or the type of somatic sexual differentiation. In relation to the fat constitution, it was found that BMI and the level of visceral fat were higher in mentally healthy individuals with MetS than in patients with schizophrenia. The analysis of the level of glucose and lipid profile in the study groups revealed that serum glucose and HDL-C levels were reduced, while TG and the atherogenic index were increased in patients with schizophrenia and MetS. The revealed changes can probably be associated with the presence of MetS risk factors specific to patients with schizophrenia.

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