

Relationship of metabolic parameters with the course of the first episode of psychosis – preliminary research

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Summary

Objectives. Cardiometabolic syndromes are the most common causes of complications shortening life expectancy in patients treated for mental disorders, especially schizophrenia. However, how much cardiometabolic risk is related to lifestyle, side-effects of treatment or psychosis is not clear. The aim of this study was a prospective assessment of metabolic changes in young, initially somatically healthy patients diagnosed with the first acute episode of psychosis with no prior pharmacological treatment.

Methods. The study involved 15 young patients (average age of 19.95 ± 6.88 years). Analyses (laboratory and clinical) were performed at the time of admission and after 3 and 12 weeks and included morphology, lipid profile, glucose, inflammation markers, blood pressure (BP), and body mass index (BMI). The severity of clinical symptoms was assessed using the *Positive and Negative Syndrome Scale* (PANSS), and the cognitive functioning was assessed using the *Montreal Cognitive Assessment* (MoCA). The duration of untreated psychosis (DUP) was also measured.

Results. There was a significant increase in BMI, dyslipidemia, inflammation, and systolic blood pressure after 12 weeks from the start of the treatment, while cortisol level decreased. A negative correlation was observed between PANSS-P (PANSS positive scale) measurements and total cholesterol, PANSS total and low-density lipoprotein, as well as DUP and MoCA. High-density lipoprotein (HDL) correlated positively with DUP, cortisol, monocytes, and white blood cells in the first week.

Conclusions. The results of the study indicate a relationship between the development and treatment of the first acute episode of psychosis and the results of laboratory tests that are indicators of the development of metabolic stress in patients.

Key words: metabolic syndrome, first-episode psychosis, dyslipidemia

Introduction

Patients suffering from schizophrenia have their life expectancy shortened by 15–20 years, mainly due to cardiovascular diseases (CVD) [1]. Metabolic syndrome, associated with cardiovascular risk, occurs in patients who suffer from schizophrenia at a rate twice as high as in the non-psychiatric population [2].

According to literature, the use of atypical neuroleptics is one of the most important factors increasing the risk of insulin resistance, dyslipidemia, and weight gain, leading to cardiometabolic complications [3–6]. The negative effects of these drugs are intensified by a number of other variables such as unhealthy lifestyle, smoking, low physical activity, and bad eating habits, especially common among patients with schizophrenia [7–9]. This may be the cause of the negative effects often associated with a lack of cooperation by patients about their strict dietary regimen or lifestyle.

Data from the literature indicate that although the effectiveness of therapy of people with first-episode psychosis (FEP) with atypical antipsychotic drugs is comparable to treatment with classic antipsychotics, an increase in cardiovascular and metabolic complications is observed among this group of patients [10]. It is not yet clear how soon the symptoms of metabolic disorders occur after the commencement of the treatment. Most authors focus in this regard on analyses in groups of older patients, often treated for a long time.

It has not been determined to what extent metabolic changes may be the result of a psychotic process and their relationship with the treatment used is only partial or apparent. In this context, potential relationships between metabolic changes and the duration of untreated psychosis and the severity of symptoms are particularly important. These issues are not the subject of systematic research, especially in the group of the youngest and the shortest-suffering patients.

The aim of the discussed study was to evaluate the cardiometabolic profile of patients with FEP and its variability during a short 12-week follow-up.

Material and methods

Study participants

The study involved 15 young patients (average age of 19.95 ± 6.88 years) admitted to the in-patient wards of the Adult, Child and Adolescent Psychiatry Clinic at the University Hospital in Krakow with a preliminary diagnosis of acute and transient psychotic disorders (F23) according to ICD-10 classification, made by a psychiatrist on the basis of a clinical examination. The selected group was characterized by relative homogeneity of race, age, and body mass index (BMI).

The exclusion criteria were: age below 15 and over 35, a history of diagnosis of any psychiatric disorder (according to ICD-10 classification), previous use of drugs associated with the risk of insulin resistance, previous use of antipsychotic or antidepressant drugs, affective symptoms accompanying the psychotic symptoms, occurrence of neurological symptoms, occurrence of cardiovascular diseases or chronic diseases,

nicotine use, abuse of psychoactive substances within 3 months before the research, inability to give informed consent to participate in the study, intellectual disability, hospitalization without consent or due to a court decision. The occurrence of affective symptoms, nicotine use and abuse of psychoactive substances as potentially exclusionary factors from the study were analyzed not only at the initial stage of the study but also throughout its entire duration.

The patients and their legal guardians who had full parental custody rights gave written informed consent to participate in the study. Blood samples needed for the first set of analyses were collected during routine material collection in the first days after admission and after 3 and 12 weeks. Patients were recruited from January 2017 to September 2018.

The Bioethics Committee of the Jagiellonian University (KBET 122.6120.23.2016) expressed a positive opinion about the study, and the director of the facility gave consent to conduct the study in the Clinical Department of Adult, Child and Adolescent Psychiatry.

Laboratory tests and therapeutic methods

After the participants were qualified for the study, 10 ml of blood was drawn from cubital fossa veins using a closed Sarstedt system. Patients were fasting all night and samples were collected between 7 and 9 a.m. Samples were stored at 4° C and transported on ice. Preparation of the material for testing began no more than 4 hours after collection. Samples with visible bilirubinemia, hemolysis, lipemia and turbidity were discarded. Routine blood tests included blood count, lipid profile (triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)), C-reactive protein (CRP), ionogram (K⁺, Na⁺, Mg⁺), glucose, cortisol, and thyroid panel (FT3, FT4, TSH). Routine laboratory tests were carried out on the day of blood collection at the clinical hospital laboratory in Krakow using the automatic Sysmex XN-2000 analyzer (Cobe, Japan) for blood count and the Cobas 6000 and Cobas 8000 biochemical analyzers (Roche Diagnostics, Mannheim, Germany) to assess biochemical and hormonal parameters. The BMI was calculated based on the height and weight parameters from 3 sets of values. Blood pressure (BP) measurements were performed between 6 and 8 a.m. according to the guidelines of the European Society of Hypertension. Detailed demographic and clinical data were collected, including duration and severity of psychotic symptoms prior to admission to hospital, accompanying somatic diseases, previous pharmacotherapy, as well as data on neuroleptic treatment and complications during hospitalization.

Assessment of the clinical condition

The severity of psychotic symptoms was assessed using the *Positive and Negative Syndrome Scale* (PANSS) [11], which describes the severity of positive symptoms (*Positive scale*, PANSS P), negative symptoms (*Negative scale*, PANSS N) and general psychopathology (*General Psychopathology scale*, PANSS G) and has an overall score

(PANSS total, PANSS T). The *Beck Depression Inventory* (BDI) was used to measure depression symptoms [12]. The assessment of cognitive functions was done using the *Montreal Cognitive Assessment* (MoCA) [13] at all time points, with the Polish basic and equivalent versions used alternately.

The study was based on two variables analyzing the pre-treatment period. An assessment of the duration of untreated psychosis (DUP) was performed, which was estimated by obtaining medical history data, i.e., the time measured from the first symptoms of psychosis until the implementation of pharmacotherapy. We also used the *Premorbid Adjustment Scale* (PAS) [14], which is a rating scale designed to assess the degree of achievement of developmental goals at individual periods of a subject's life before the onset of clinical symptoms of psychosis. The PAS consists of the following subscales: C – associated with childhood, EA – early adolescence, LA – late adolescence, A – adulthood, G – general, T – total score.

Treatment and diagnosis stability

Pharmacotherapy was prescribed and continued for all patients involved in the study in accordance with the guidelines of the American Psychiatric Association for the treatment of acute psychosis [15]. Classic and atypical neuroleptics were used in the treatment as mono – and polytherapy. The pharmacotherapy was also modified during the 3-month treatment period. A total of 6 different neuroleptics were used in the study group, including haloperidol, olanzapine, risperidone, quetiapine, and clozapine. Therapeutic doses did not exceed the recommended dose range. Besides pharmacotherapy, the patients were provided with psychological support.

At 12 weeks from the beginning of treatment, a diagnosis of schizophrenia according to the criteria of ICD-10 was confirmed in 13 patients. None of the patients were excluded from the study because of affective symptoms, nicotine use or abuse of psychoactive substances.

Statistical analysis

The comparison of quantitative variables obtained by three repeated measurements was performed by Analysis of Variance (ANOVA) for repeated measurements (when the variable had a normal distribution) or Friedman's test (otherwise). After the detection of statistically significant differences, post-hoc analysis was performed using the paired Student's t-test or the paired Wilcoxon's test (in the case of a lack of normality) in order to identify statistically different groups. Bonferroni correction was used in both cases. Correlations between quantitative variables were analyzed using Pearson's or Spearman's correlation coefficients. The strength of dependency was interpreted according to the following scheme: $|r| \geq 0.9$ – very strong; $0.7 \leq |r| < 0.9$ – strong; $0.5 \leq |r| < 0.7$ – moderately strong; $0.3 \leq |r| < 0.5$ – weak; $|r| < 0.3$ – very weak (negligible). The analysis was carried out with the R program, version 3.5.2 [16].

Results

The results of 15 patients (9 women and 6 men with a mean age of 19.95 ± 6.88 years) were analyzed. There were no statistically significant age differences between men and women.

The results of PANSS at three time points are presented in Table 1. After 3 months of treatment, in both women and men, significantly lower PANSS values were observed compared to the other two time points.

Table 1. Results of the PANSS examination during 12 weeks of observation (differences between the 1st, 3rd, and 12th weeks of the study) in the group of women and men

Parameter		Women (N = 9) Mean \pm SD	Men (N = 6) Mean \pm SD	p^a
Age		20.22 \pm 6.69	19.67 \pm 7.06	0.718
Positive scale (P)	1st week	19.89 \pm 8.12	25.17 \pm 11.14	0.218
	3rd week	21.22 \pm 11.62	28.67 \pm 12.4	0.257
	12th week	11.33 \pm 6.3	15.5 \pm 9.71	0.498
Negative scale (N)	1st week	16.78 \pm 9.55	22.83 \pm 9.79	0.255
	3rd week	16.89 \pm 11.57	23.17 \pm 14.51	0.308
	12th week	10.56 \pm 7.04	15.17 \pm 9.6	0.308
General psychopathology scale (G)	1st week	38.44 \pm 13.13	47.33 \pm 18.13	0.308
	3rd week	37.44 \pm 18.43	47.83 \pm 22.59	0.168
	12th week	20.1 \pm 1.45	20.33 \pm 1.37	0.771
Total scale (T)	1st week	75.11 \pm 30.23	95.33 \pm 38.85	0.168
	3rd week	75.56 \pm 41.49	99.67 \pm 49.44	0.168
	12th week	42 \pm 13.69	51 \pm 19.87	0.308

p^a – lack of normality of distribution in groups, Mann-Whitney test

The average results of the *Premorbid Adjustment Scale* (PAS) are found in Table 2.

Table 2. Results of the PAS

PAS test	Mean \pm SD
C scale (childhood)	0.59 \pm 0.13
EA scale (early adolescence)	0.55 \pm 0.16
LA scale (late adolescence)	0.55 \pm 0.21
A scale (adulthood)	0.24 \pm 0.36
G scale (general)	0.6 \pm 0.08
T scale (total)	2.65 \pm 0.57

The average DUP value in the subjects was equal to 3.23 ± 3.26 months. The BDI values were significantly different between the first observation (23.93 ± 13.1) and the results in the third week of the study (15.33 ± 11.34), then decreasing in the 12th week to a value of 7.93 ± 6.52 ($p < 0.001$, Wilcoxon paired tests with Bonferroni correction).

MoCA values in patients were significantly higher (21.07 ± 2.74) after 3 months when compared to the admission period (13.73 ± 2.79 ; $p < 0.001$, paired t-test).

Significant changes in laboratory parameters were observed, as summarized in Table 3.

Table 3. Results of parameters routinely diagnosed at the Department of Child and Adolescent Psychiatry

Parameter	1st week Mean \pm SD	3rd week Mean \pm SD	12th week Mean \pm SD	p ^a
WBC [1000/ μ L] ^b	6.86 \pm 1.83	7.17 \pm 2.14	8.98 \pm 3.47	0.062
RBC [mln/ μ L]	4.81 \pm 0.35	4.69 \pm 0.33	4.3 \pm 0.46	0.004 1w, 3w > 12w
HGB [g/dL]	14.04 \pm 1.05	13.69 \pm 1.27	13.56 \pm 2.85	0.013 NA
HCT [%]	41.63 \pm 2.59	40.21 \pm 3.13	39.29 \pm 3.67	0.072
MCV [fL]	87.17 \pm 4.05	86.44 \pm 4.13	87.04 \pm 3.88	0.374
MCH [pg]	29.55 \pm 1.59	29.62 \pm 1.6	29.91 \pm 2.06	0.671
MCHC [g/dL]	34.02 \pm 1.25	34.31 \pm 1.33	34.16 \pm 2	0.607
PLT [1000/ μ L]	251.33 \pm 55.27	223.6 \pm 52.97	221.57 \pm 58.48	0.121
RDW-SD [fL]	41.13 \pm 2.21	40.4 \pm 2.9	39.92 \pm 2.44	0.223
RDW-CV [%]	12.96 \pm 0.79	12.83 \pm 0.91	12.81 \pm 0.76	0.498
PDW [fL]	13.09 \pm 1.71	12.39 \pm 1.48	12.86 \pm 1.52	0.315
MPV [fL]	10.55 \pm 0.8	10.33 \pm 0.73	10.34 \pm 1.01	0.564
P-LCR [%]	29.61 \pm 7.1	27.89 \pm 6.4	27.81 \pm 6.65	0.536
NEU [1000/ μ L]	3.78 \pm 1.6	3.51 \pm 1.68	4.72 \pm 3.58	0.807
LYM [1000/ μ L]	2.36 \pm 0.94	2.29 \pm 0.86	2.51 \pm 1.03	0.502
MONO [1000/ μ L]	0.58 \pm 0.18	0.63 \pm 0.27	0.78 \pm 0.38	0.044 NA
TG [mmol/L] ^b	1.05 \pm 0.4	1.27 \pm 0.41	1.83 \pm 0.62	< 0.001 12w > 3w, 1w
LDL [mmol/L] ^b	2.32 \pm 0.78	2.76 \pm 1.11	3.12 \pm 0.99	< 0.001 12w > 1w
TC [mmol/L] ^b	4.11 \pm 1.18	4.83 \pm 1.22	5.17 \pm 1.12	< 0.001 12w, 3w > 1w

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GLU [mmol/L]	5.1 ± 1.24	5.19 ± 0.52	5.12 ± 0.68	0.319
TSH [μIU/mL]	2.5 ± 0.92	2.67 ± 0.97	2.72 ± 1	0.198
HDL [mmol/L] ^b	1.59 ± 0.38	1.44 ± 0.32	1.1 ± 0.37	< 0.001 1w, 3w > 12w
CRP [mg/L] ^b	3.2 ± 6.32	5.82 ± 11.53	7.21 ± 13.96	0.028 NA
Weight [kg]	62.93 ± 11.16	65.39 ± 11.33	67.39 ± 12.77	0.001 12w, 3w > 1w
BMI [kg/m ²]	22.29 ± 3.01	23.27 ± 3.15	24 ± 3.9	0.001 12w, 3w > 1w
CORTISOL [μg/dL]	15.99 ± 4.6	14.88 ± 4.6	13.98 ± 4.44	0.001 1w > 3w > 12w
SBP [mmHg]	121.87 ± 9.65	124.6 ± 7.44	135.4 ± 10.4	0.001 12w > 3w, 1w
DBP [mmHg]	82.4 ± 9.19	83.13 ± 11.21	87 ± 8.49	0.288

^a NP – lack of normality of distribution in at least one measurement, Friedman's test + post-hoc results (Wilcoxon test for pairs associated with Bonferroni correction); p – normal distribution in all measurements, repeated measurement ANOVA + post-hoc analysis results (Student's t-test for pairs associated with Bonferroni correction); w – week of observation.

^b The results of CRP, lipid profile and WBC are a part of the study on the role of the endothelium in peripheral vascular insufficiency in patients with FEP [17].

The concentrations of TC, TG, and LDL were significantly higher at 3 weeks and 3 months after admission to the hospital. The CRP level increased until the 12th week, when it reached the highest value. The values of other parameters, such as body mass and BMI, were significantly lower in the first week than at the other two time points. The opposite linear relationship was demonstrated for cortisol and TSH levels.

In the course of the study, a statistically significant increase in the value of systolic blood pressure (SBP) was obtained at three time points. Values in the first week were statistically significantly lower than in the third week and the third month of the study (Table 3).

As presented in Table 4, DUP correlated significantly and negatively with MoCA in the first week of the study. Positive significant correlations also occurred between DUP and BDI, PAS-EA and PAS-G. BDI also significantly and positively correlated with HDL levels. A significant positive relationship was found between SBP and HDL levels in the first week of the study.

Table 4. Relationship between psychological assessment, clinical examination, and the results of laboratory tests in the first week of the study

Variable	r	p-value
DUP		
PAS-G	0.593	0.020
MoCA	-0.781	0.001
BDI	0.872	< 0.001
PAS-EA	0.653	0.008
HDL		
BDI	0.657	0.008
PAS-EA	0.603	0.017
PAS-G	0.527	0.043
SBP	0.606	0.022
LDL		
PAS-LA	0.617	0.014
PAS-T	0.691	0.004
TC		
PAS-T	0.680	0.005

During the first week after the diagnosis, there was a strong positive correlation between PANSS P and TC, as well as between PANSS total and LDL. There were statistically significant positive correlations between LDL and LA in the PAS scale, and between the T and G subscales of PAS in the first week of the study. The T subscale of PAS (PAS-T) also showed a significant positive correlation with TC.

Significant positive dependencies were obtained between DUP and the levels of cortisol in the first, third and twelfth week of the study. Cortisol levels correlated significantly and moderately with white blood cell (WBC) levels in the 1st week and with HDL levels in the 12th week. Cortisol level in the 12th week was significantly lower than in the 1st week.

There were significant positive correlations between the DUP and serum concentration levels of monocytes, and between cortisol and WBC levels. There was a positive correlation between glucose and hematocrit levels as well as red blood cell count, and BMI.

Correlations between clinical and psychological symptoms and routinely performed laboratory tests such as TC, LDL, and monocyte levels are shown in Table 5.

Table 5. Selected significant correlations between routinely performed laboratory tests and clinical symptoms at particular time points

Variable	1st week		3rd week		12th week	
	r	p	r	p	r	p
PANSS T scale						
LDL ^a	0.657	0.008	0.528	0.043	-	-
TC ^a	0.678	0.005	-	-	-	-
MONO	-0.686	0.005	-	-	-	-
PANSS N scale						
MONO	-0.744	0.001	-	-	-	-
PANSS P scale						
LDL ^a	0.612	0.015	-	-	-	-
TC ^a	0.731	0.002	-	-	-	-
MONO	-0.530	0.042	-	-	-	-
PANSS G scale						
LDL ^a	0.631	0.012	0.607	0.016	-	-
TC ^a	0.681	0.005	-	-	-	-
MONO	-0.610	0.016	-	-	-	-
MoCA						
TG	-	-	0.620	0.014	-	-
LDL	-	-	-	-	-	-
HDL	-	-	-	-	-	-
TC	-	-	-	-	-	-
WBC						
TC	0.664	0.007	-	-	-	-
MONO	0.663	0.007	-	-	-	-
CRP ^a	0.617	0.019	-	-	-	-
DUP						
CORTISOL	0.838	<0.001	0.749	0.001	0.626	0.012
MONO	0.635	0.011	0.722	0.002	-	-
HDL	-	-	0.614	0.015	0.566	0.035
MoCA	-0.781	0.001	-0.645	0.009	-	-
BDI	0.872	<0.001	0.873	<0.001	0.524	0.045
Cortisol						
WBC	0.515	0.049	-	-	-	-
HDL	-	-	-	-	0.804	0.001

^aThe results of CRP, lipid profile and WBC are a part of the study on the role of the endothelium in peripheral vascular insufficiency in patients with FEP [17].

Discussion

This prospective study concerned cardiometabolic risk assessment in young patients diagnosed with FEP. Noticeable improvement in both clinical status and PANSS scores was observed in young women and men with FEP. This is in accordance with the results of Segarra et al [18]. Significant interactions were found regarding individual subscales related to positive, negative and general symptoms of the PANSS scale, with more pronounced improvement for men than for women. These results coincide with those of García-Bueno et al. [19], Lang et al. [20] and Kinson et al. [21].

The study also explored the relationship between premorbid adaptation and cardiometabolic markers at the beginning of psychotic decompensation. It shows that the worse the obtained results by the patients in all four age periods on the *Premorbid Adjustment Scale* (PAS) were, the greater the deterioration of the parameters in the lipid profile was observed. The more the patients withdrew and had fewer connections with others, and the worse they functioned outside the generational family and were unable to build intimate socio-sexual relationships, the more they presented deteriorated metabolic results at the onset of the first symptoms of psychosis. This marks the importance of health education and diagnostic monitoring of metabolic indicators in this group of patients from the first weeks of treatment. Our research also shows the importance of psychosocial adjustment for the level of LDL cholesterol in late adolescence, i.e., a particular period of human development, the period of high sensitivity and vulnerability.

These results can be interpreted in two ways. The measure used can describe the presence of prodromal symptoms in the areas of social relations in the studied patients. In this context, the observed result can be interpreted similarly to relationships with DUP. It may also indicate the importance of social relations from early childhood for health in a group of people with the first episode of psychosis. Psychosocial maladjustment can worsen cardiometabolic indicators at the behavioral (e.g., low physical activity, smoking, poor diet) and biological (e.g., stress response) level. Social isolation and loneliness are a common source of chronic stress [22] causing an increase in blood pressure [23], activation of the hypothalamic-pituitary-adrenal (HPA) axis [24] and sympathetic nervous system [25], and contributing to the development of coronary atherosclerosis [26]. In the face of stress, the body tries to adapt to the existing conditions, including through enzymatic reactions that gradually remove reactive oxygen or nitrogen species. In this situation, efficient cell antioxidant systems are strengthened to even out intracellular levels of NADPH and reduced glutathione. Overexpression of pro-inflammatory genes and antioxidant enzymes, i.e., superoxide dismutase (SOD), among others, constitutes the answer that roughly illustrates the anti-inflammatory strategy, aimed at combating oxidative stress (removal of oxygen and nitrogen radicals arising primarily as a result of oxygen metabolism). Chronic social stress causes leukocytosis, glucocorticoid resistance, increased expression of pro-inflammatory genes and induces oxidative stress in the CNS and peripheral tissues [27]. There is also a significant interaction between social isolation and cholesterol reactivity to stress (greater social isolation is associated with a greater total/HDL cholesterol response to stress) [28].

Regardless of the direction of interpretation, the obtained results testify to the relationship between the somatic state and the social context in which patients with the first psychotic episode function.

The explanation of the observed changes in the lipid profile in the discussed study may be due to the fact that high levels of LDL promote the formation of oxidized forms of these lipoproteins and lead to the development of atherosclerotic plaque. Nettis et al. [29] obtained similar (to ours) mean LDL concentrations in FEP patients. However, we observed a significant difference in TG levels. This correlates with LDL values whose mean concentrations were significantly lower at the first test point as compared to the third. These results are confirmed by mean LDL concentrations from the study by Nettis et al. [29]. HDL concentrations also changed over time in a statistically significant manner, showing an inversely linear relationship with LDL and TC. Gjerde et al. [30] demonstrated mean HDL values of 1.39 ± 0.40 mmol/L at the beginning of psychosis, which decreased to 1.32 ± 0.37 mmol/L after 12 weeks, similar to our results.

The potential anti-atherogenic effect of HDL is associated not only with stimulation of cholesterol transport from cells, but also with anti-inflammatory, antioxidant, anticoagulant, and diastolic arterial activity. Despite the numerous anti-apoptotic HDL effects described, high plasma concentrations do not always (and not in all patients) protect against the development of atherosclerotic lesions. These studies, as well as the results of positive correlation of HDL with TC, monocytes, and cortisol obtained by the authors, lead to the suggestion that not all HDL particles have a protective effect. Inflammation leads to significant modifications in HDL molecules, characterized by the lack of antioxidant enzymes, paraoxonase-1 and glutathione peroxidase, which inhibit LDL oxidation. Disorders in lipid metabolism during the long duration of the body's defense reaction take on the nature of a chronic inflammatory response manifested by an increased level of CRP as well as other cytokines (IL-1, IL-6, IL-8, TNF- α) which constitute the so-called secondary signal transducers involved in the regulation of pro-inflammatory gene expression [31].

The obtained cortisol result and its inversely proportional relationship with CRP is one of the important observations of the study. The level of cortisol in the first week of observation was inversely proportional to CRP, the marker of inflammation, silencing the inflammatory process at the beginning of the disease. There was an increased level of CRP at the end point of observation when a linear decrease in cortisol levels was observed. Increased cortisol level in schizophrenia can be associated with excessive morbidity and mortality in the group that develops the metabolic syndrome [32]. Hypercortisolism leads to hypertension, central obesity and disorders of lipid metabolism. The decrease in cortisol levels over time can also be explained by the action of second-generation neuroleptics, which reduce cortisol in the blood [33, 34]. In our study, a statistically significant increase in the CRP level was observed which reached the reference values established for a healthy population (<5 mg/L), intensifying the inflammation taking place in the bodies of the patients. The results obtained in this study provide evidence of the primary role of inflammation in the initiation and progression of cardiovascular complications in the early stages of schizophrenia.

The study showed an increase in absolute body weight and BMI. A more sedentary lifestyle during hospitalization may also have an important influence on these parameters. Increase of body mass and BMI, although relatively small in the observed time interval, is a disturbing phenomenon.

A relationship between the increase in BMI during antipsychotic treatment and the partial improvement of cognitive functioning was found. It should be noted that similar observations do appear in the subject literature [35]. The described effects may be related to the use of pharmacotherapy. Research suggests that it is mainly atypical antipsychotic drugs that improve cognitive function in patients with psychosis. This is due to their mechanism of action on dopaminergic, noradrenergic, and serotonergic systems [36]. The release of serotonin is of particular importance as it blocks the 5HT receptor, thereby inducing both weight gain [37] and improvement of cognitive functions [38]. The altered glucose metabolism due to impaired insulin signaling, co-occurring with clinical improvement during pharmacological treatment of schizophrenia, is also of significance [39]. Weight gain promotes increased insulin outflow, which in turn improves cognitive function [40].

The mechanism, underlying the increased body weight and metabolic changes in psychotic patients receiving second-generation neuroleptics, involves changes in glucose and lipid metabolism as co-occurring phenomena. One of the main mechanisms, explaining the formation of both short-term and long-term small for gestational age (SGA)-induced obesity, is associated with the blockade of hypothalamic histamine-1 (H1), serotonin 2A and 2C (5HT2A, 5HT2C), α adrenergic, muscarinic M3 and dopaminergic D2 receptors responsible for increased appetite [41, 42].

The mechanisms leading to dyslipidemia are still not completely clear. One of the potential pathways leading to metabolic dysregulation through increased serum TG and cholesterol levels is the inhibition of TG hydrolysis and the effect on the increase of hepatic TG secretion [5]. As indicated in the literature on the subject, the participation of peroxisome proliferator-activated receptors (PPAR) in the control of fatty acid metabolism by regulating their transport and metabolism, is a probable mechanism involved in the lipid imbalance [43]. The role of sterol regulatory element-binding proteins (SREBP) is also underlined. These proteins (mainly SREBP-1 and SREBP-2) play a significant role in the biosynthesis of lipids. It is known from the available literature that atypical neuroleptics interfere in biochemical pathways by increasing the expression of SREBP-1 and SREBP-2 protein genes, thereby causing lipid accumulation in the liver and increased lipid synthesis [44].

Pharmacotherapy may be a decisive factor for the observed changes in BP as well. Although the effect of atypical neuroleptics on the BP level is not fully understood, it is known that dopamine D2 receptors, which are the main targets of these drugs in the central nervous system, are also present on peripheral organs essential for pressure regulation. Blockade of D1 and D2 receptors present in the kidneys by atypical neuroleptics may thus be one of the mechanisms leading to the development of hypertension [45, 46]. The results of this study provide confirmation of the assumptions regarding the association of atypical neuroleptics with an increase in BP values. Except for HDL, however, no significant relationship was found between

the increase in BP and biochemical parameters (lipid profile, CRP) at specific time points. The lack of association between BP increase and inflammation index (CRP), body weight and BMI, lipid profile and cortisol confirms previous observations regarding the effect of atypical neuroleptics on BP through their interaction with peripheral receptors.

Conclusions

The obtained results indicate the presence of a number of complex metabolic interactions associated with development of symptoms of schizophrenia and the course of its treatment. These dependencies are observed in the first days of treatment and change dynamically in the following weeks of pharmacotherapy.

Given the huge burden of CVD and early mortality in schizophrenia, screening, and subsequent prevention and treatment of metabolic complications in this population at an early stage of the disease seems justified.

Limitations

The study has several important limitations, including a relatively short duration of the study and a small sample size, which limit the conclusions on modulation of the influence of pharmacotherapy on the analyzed parameters. The use of BMI, rather than an assessment of waist circumference as a more measurable indicator of obesity, is an additional limitation. Moreover, the subjects had a low baseline BMI that could affect the results. The study did not include a control group, which means that the obtained results cannot be analyzed in relations to, for example, patients with other psychiatric diagnoses undergoing similar pharmacological treatment.

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