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Improvement in clinical symptoms in patients with the first episode of psychosis is associated with a decrease in systemic nitric oxide availability. A pilot study

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Summary

Objective. The aim of the study was to assess the relationship between the improvement of the clinical condition of patients with the first episode of psychosis (FEP) and changes in nitric oxide (NO) plasma concentration based on the level of its metabolites NO_2^- and NO_3^-, as well as changes in lipid profile and biomarkers of systemic inflammation.

Method. The study was carried out in a group of 25 young patients with FEP (aged 14–35). Blood samples were collected in the 1st and 12th week after admission to the hospital to assess NO metabolites, lipid profile and inflammatory biomarkers. Demographic and clinical data were also analysed.

Results. In the study group, three months after admission to the hospital, an improvement in the clinical symptoms was observed, as evidenced by a decrease in the *Positive and Negative Syndrome Scale* (PANSS) scores. This improvement was associated with a decrease in the plasma nitrite concentration, a deterioration of the lipid profile and the activation of systemic inflammation. Interestingly, in the 1st week after the hospital admission, a longer duration of untreated psychosis (DUP) was associated with a lower NO_2^- plasma concentration, and a higher intensity of positive symptoms (*PANSS Positive Symptoms Scale*) was associated with higher CRP plasma level.

Conclusions. Our results suggest that adverse metabolic response, systemic inflammation and a fall in systemic NO bioavailability represent early systemic manifestations of FEP that are not controlled by short-term anti-psychotic treatment and may pose cardiovascular risk.

Key words: first-episode psychosis, vascular endothelium, nitric oxide

Introduction

Schizophrenia is a mental disorder accompanied by a high risk of premature death, where the mortality rate is two to three times higher than that in the general population [1]. Cardiovascular events are the most common cause of premature death in this group [2]. Considering the key role of the vascular endothelium in the proper functioning of the cardiovascular system [3] and the importance of endothelial dysfunction in the development of cardiovascular diseases including atherosclerosis [4], increased cardiovascular risk in patients suffering from schizophrenia could therefore possibly be related to the accelerated development of systemic endothelial dysfunction.

To date, only several reports have discussed the impaired function of the peripheral vascular endothelium in patients suffering from schizophrenia. Israel et al. [5] were the first to show that microcirculation reactivity and post-occlusive reactive hyperaemia (PORH), as measured by laser Doppler flowmetry (LDF), were blunted in the untreated patients suffering from paranoid schizophrenia as compared to the matched control group. Even though the studied groups were rather small (n = 21), the observed difference was significant, suggesting the profound effects of acute psychotic decompensation on the peripheral microcirculation and endothelial function. Another study [6], involving a cohort of 83 patients mostly (77%) treated with atypical antipsychotics, found that approximately 50% of schizophrenia subjects met the criteria of endothelial dysfunction (RH < 1.67), as assessed by reactive hyperaemia – peripheral artery tonometry (RH-PAT) [7]. Afterwards, in a bigger cohort of patients (n = 203) treated with atypical antipsychotics, it was revealed that roughly 48% of the patients had endothelial dysfunction (RH < 1.67) and approximately half of the patients had metabolic syndrome [8]. A number of other studies confirmed the association between schizophrenia and peripheral endothelial dysfunction, including studies on microcirculation [9] and peripheral microvascular function as measured by the velocity time integral (VTI) [10]. Some researchers, however, did not identify the impaired endothelial function in patients with schizophrenia using a non-invasive peripheral RH-PAT approach [11].

Interestingly, in contrast with the impaired RH-PAT outcomes reported in schizophrenic patients, brachial arterial flow-mediated vasodilation (FMD) — a gold standard method designed to assess conduit vessel endothelial function — did not display an impairment [10]. This result suggests more pronounced or earlier endothelial dysfunction in microcirculation than in conduit-type vessels in patients with schizophrenia.

Furthermore, various biomarkers of endothelial dysfunction have been identified in schizophrenic patients, including elevated von Willebrand factor (vWF) [12],

soluble fms-like tyrosine-kinase-1 (sFlt-1) [13] and reduction of the bioavailability of nitric oxide (NO) [14]. Nitric oxide is a compound with a half-life of 5 seconds, which makes it very chemically unstable [15]. It is extremely quickly oxidised to nitrites and nitrates. Therefore, a direct determination of NO in plasma of patients is not possible, and the assessment of the bioavailability of nitric oxide in vivo is normally based on the measurement of its transformation products: NO_2^- and NO_3^- ions [16].

The concentration of NO metabolites in plasma reflects the endothelial function [17] and thus could represent a biomarker of peripheral vascular dysfunction in schizophrenia. However, the measurements of nitrites and nitrates in psychotic patients did not yield concordant results. Das et al. [18] found lower plasma levels of nitrates in patients with first-episode psychosis (FEP), while Noto et al. [19] did not observe a difference between plasma concentrations of metabolites of nitric oxide in the drug-naive FEP patients and the healthy group.

Despite the evidence of the coexistence of schizophrenia and peripheral endothelial dysfunction, the mechanisms involved in this relationship are still not clear.

Therefore, the aim of this preliminary prospective observational study was to determine whether the short-term improvement in major psychotic symptoms in response to antipsychotic therapy in young patients with FEP is associated with changes in the endothelial function, through the assessment of changes in plasma concentrations of NO metabolites, markers of systemic inflammation (CRP) and the lipid profile.

Patients and methods

Selection of patients and clinical data analysis

This study included 25 patients aged 14 to 35 years who were admitted to the child and adolescent psychiatric ward and the adult psychiatric ward at the Clinical Department of Adult, Child and Adolescent Psychiatry at the University Hospital in Krakow, diagnosed with acute polymorphic psychotic disorders (F23) according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) [20]. The diagnosis was made by a psychiatrist based on the findings of a clinical examination at the time of admission to the ward. The study enrolment occurred from January 2017 to December 2019. Exclusion criteria included: (1) the inability to express individual consent, (2) an intellectual disability, (3) hospitalisation without consent or due to a court order, (4) occurrence of cardiovascular diseases, (5) abuse of psychoactive substances or smoking during the three months before the examination, (6) accompanying affective symptoms.

The laboratory samples needed for the first set of analyses were collected during routine material collection in the first days of hospitalisation, as well as three months after the start of the study.

Demographic and clinical data were collected from each patient qualified for the study, including an accurate history of admission, duration and severity of pre-admission psychotic symptoms (duration of untreated psychosis – DUP), previous

pharmacotherapy and stimulant use, disease severity and treatment with neuroleptics during the hospital stay (at subsequent time point). The degree of severity of psychotic symptoms was assessed using the *Positive and Negative Syndrome Scale* (PANSS) [21] during the first week and the third month after admission to the hospital due to acute psychotic decompensation. The PANSS consists of 30 items divided into 3 subscales: *Positive Symptoms* (PANSS P), *Negative Symptoms* (PANSS N) and *General Psychopathology* (PANSS G). In addition, the overall score (*PANSS – Total*; PANSS T) can be determined.

The body mass index (BMI) was calculated and the systolic and diastolic blood pressure (SBP, DBP) were measured.

Blood samples were taken from 25 enrolled fasting patients between 6 am and 8 am. Routine laboratory blood tests included complete blood count (white and red blood cell counts), lipid profile (low-density and high-density lipoproteins (LDL and HDL), triglycerides (TG), and total cholesterol (TC)), an inflammation marker (C-reactive protein – CRP), ionogram (K^+, Na^+, Mg^{2+}), glucose, creatinine, urea, γ-glutamyltransferase (GGTP), and a thyroid hormone panel (free T3, free T4, and thyroid-stimulating hormone).

Routine analyses were carried out on the day of blood collection at the clinical hospital laboratory in Krakow using automatic XN-2000 analysers (Sysmex Corp., Kobe, Japan) to determine complete blood count and biochemical Cobas 6000 and Cobas 8000 analysers (Roche Holding AG, Basel, Switzerland) to assess the biochemical parameters and thyroid hormones. The clinical hospital laboratory in Krakow is routinely put through a daily internal quality control procedure (Precicontrol ClinChem Multi 1, P Precicontrol ClinChem Multi 2, Lyphochek Assayed Chemistry Control level 1, Lyphochek Assayed Chemistry Control level 2, Precicontrol Universal level 1 and Precicontrol Universal level 2 for biochemical parameters; Sysmex XN-Check on three levels for complete blood count) and systematic external quality control (at the Centre for Quality Monitoring in Laboratory Medicine, Poland and Randox International Quality Assessment Scheme) in accordance with the European Union directive on laboratory examinations.

Analyses of nitric oxide metabolites

Blood samples were collected in the 1st and 12th week after admission to assess changes in NO plasma concentration based on the level of its metabolites, NO_2^- and NO_3^-. Blood was collected from patients into test tubes containing heparin as an anticoagulant. Plasma was separated from the blood after centrifugation (450 × g, 4°C, 10 min) and stored at – 80 °C for further analysis. The concentrations of nitrites (NO_2^-) and nitrates (NO_3^-) in plasma samples were measured with an ENO-20-NOx analyser (Eicom Corp., San Diego, CA, USA) based on a liquid chromatography method with a post-column derivatisation using Griess reagents. The metabolites NO_2^- and NO_3^- were separated on a NO-PAK column (4.6 × 50 mm; Eicom Corp., San Diego, CA,

USA) and NO_3^- was reduced to NO_2^- on a cadmium-copper column (NO-RED; Eicom Corp., San Diego, CA, USA). Thereafter, NO_2^- was mixed with the Griess reagent in a thermostated reaction coil (35°C). The absorbance of formed diazo derivatives was measured at a wavelength of 540 nm. The flow rate of the mobile phase (Carrier Solution) was 330 µL/min, whereas the flow rate of the Griess reagent (Reactor Solution) was 110 µL/min. Plasma samples were precipitated with methanol at a ratio of 1:1 (v/v), centrifuged at 10,000 × g for 10 minutes, and 10 µL of supernatant was subjected to direct analysis. The linearity range for NO_2^- was 0.02 to 500 µmol/L, and that for NO_3^- was 0.2 to 500 µmol/L. The applied method was characterised by an accuracy of ±15% (85%–115%) and a precision of less than 15%.

Statistical analysis

The significance of the t-test comparisons was determined on the basis of the confidence intervals calculated by the *bootstrap* method based on 2,000 samples and after adjusting the limits of the confidence intervals with the Bonferroni correction for the number of tests. Assuming the alpha significance level at 0.05 for all analyses, after the correction 99.7% confidence intervals for the performed tests were established. Correlations were analysed using Spearman's correlation coefficients. In order to correct for the number of comparisons, the Benjamini-Hochberg procedure was used. Significance level was assumed to be equal to 0.25. The analyses were performed with the IBM SPSS 26 package. The charts were made in the R environment [22] using the tidyverse package [23].

Results

Clinical characteristics of patients

The study involved 25 patients with FEP, including 15 women and 10 men, assessed at two time points (during the first week of treatment and three months thereafter). The median age of patients at the time of enrolment was 18.88 years (SD 5.59, min. 14, max. 35). There was no significant age difference between women and men.

The median DUP was 8.92 weeks (SD 11.21, min. 1, max. 48).

In accordance with the ICD-10 criteria, all 25 patients were diagnosed with an episode of acute polymorphic psychotic disorder (F23). No patient had a history of psychoactive substance or tobacco use (e.g., cigarettes; e-cigarettes; cigars; cigarillos; chewing tobacco; pipe tobacco; or HEETS™ cigarettes from Philip Morris International, New York, NY, USA). None of the patients were diagnosed with comorbidities that could significantly affect their cardiovascular health (metabolic syndrome or hypertension in particular). The subjects had not been treated with neuroleptics before admission to the hospital.

The study group was relatively homogeneous in terms of age when the first symptoms of the illness appeared, symptomatology, health care needs, applied treatment

methods, comorbidities, and the toxicological load that was acceptable taking into account the inclusion and exclusion criteria.

Treatment used

Classical and atypical neuroleptics were used in adjusted doses, including haloperidol in 16 patients, olanzapine in 6 patients, quetiapine in 3 patients, and a combination of haloperidol and olanzapine in one patient during the first week of admission. However, during the three-month treatment phase, the pharmacotherapy was modified. In the third month of the study, only second-generation neuroleptics were used. Five patients received olanzapine monotherapy, six received quetiapine, two received risperidone monotherapy, and one patient received a combination of olanzapine and risperidone. Two patients were treated with a combination of olanzapine and aripiprazole, three with a combination of olanzapine and quetiapine, and two with a combination of quetiapine and aripiprazole. During the third month of the study, three patients were receiving clozapine. In order to conduct the analyses, the doses of the drugs used were converted into the chlorpromazine equivalent [25]. The median dosage in terms of chlorpromazine in the first week of treatment amounted to 180 mg (SD 73.6, min. 50, max. 300), and in the third month to 470.67 mg (SD 256.1, min. 200, max. 1200).

Change in clinical status

After three months of treatment, significantly lower values of all PANSS subscales were observed as compared to the respective values in the first week after the hospital admission (Fig. 1, Fig 4).

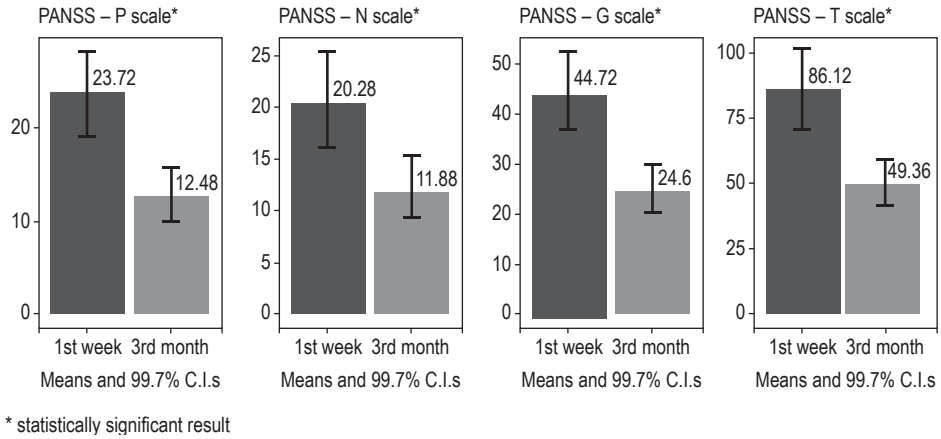
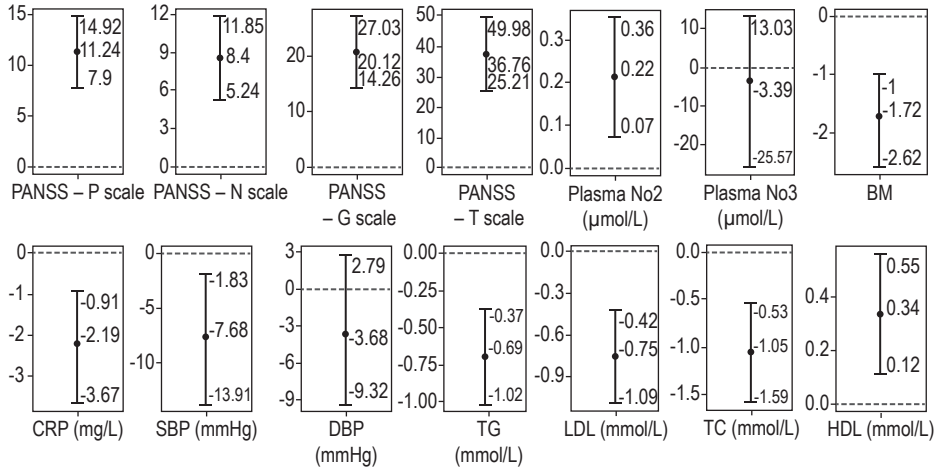


Fig. 1. **Change in clinical status (PANSS subscales)**

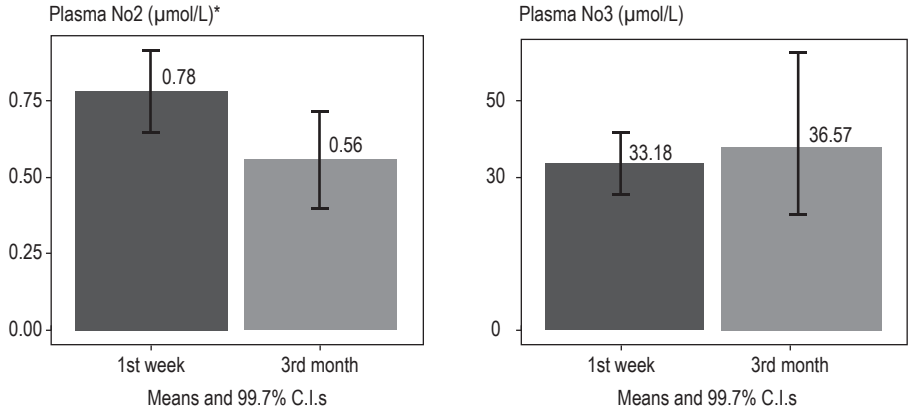


Mean difference between measurements at 1st week and 3rd month with bootstrapped 99.7% confidence intervals. Significant results do not include zero (marked with intermittent line).

Fig. 4. **Changes in studied variables between the first week and third month – Student's t-test with Bonferroni correction**

Changes in the concentration of NO metabolites in plasma

In the study group, a statistically significant decrease in the concentration of NO_2^- in plasma was noted three months after the patients were admitted to the hospital, as compared to the concentrations of NO_2^- in the first week (Fig. 2, Fig. 4).



* statistically significant result

Fig. 2. **Changes in the concentration of the NO metabolites**

Changes in BMI, BP, CRP and lipid profile

A statistically significant increase in BMI and SBP was observed in the third month after the hospital admission when compared to the first measurement recorded. Plasma CRP also increased in the third month after the patient admission to the hospital. The concentrations of TC, TG, LDL in plasma were higher in the third month when compared to the first measurement recorded. On the other hand, three months after the patients were admitted to the hospital, a decrease in HDL concentration was noted (Fig. 3, Fig. 4).

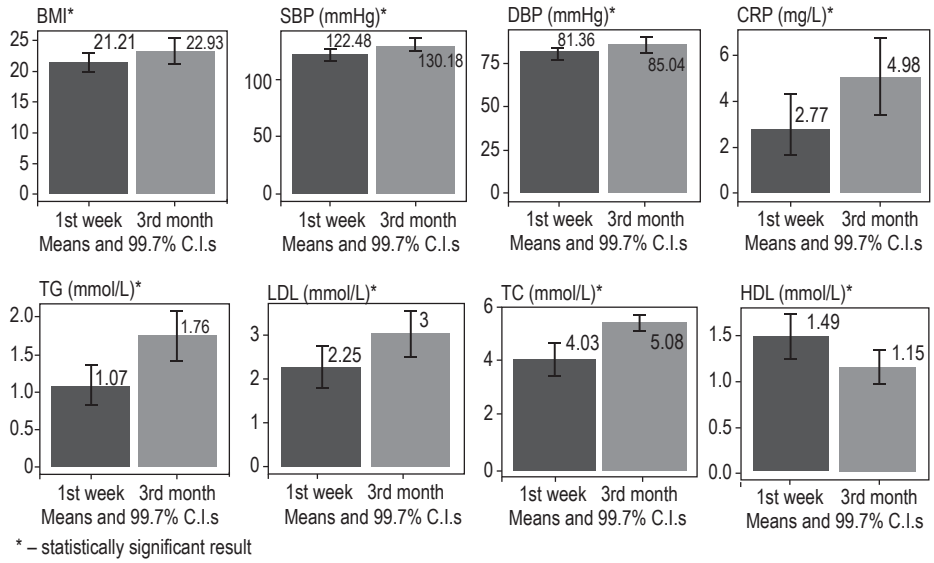


Fig. 3. **Changes in BMI, BP, CRP and lipid profile**

All of the above t-tests without Bonferroni correction led to similar results as in the case of analyses with its application.

Relationship between the DUP, PANSS subscales and studied variables

The correlations between DUP and PANSS and the measured variables were analysed. After introducing the Benjamini-Hochberg correction, the statistical significance of the correlation of NO_2^- from the first week with DUP (-0.441*, $p = 0.027$) was observed.

A number of statistically significant correlations were noted between the PANSS scales from the first week and the third month, and the studied variables (Table 1).

Table 1. **Correlation between PANSS subscales and the studied variables in the first week and the third month after the patients' hospital admission**

PANSS / Variables	PANSS–P scale	PANSS–N scale	PANSS–G scale	PANSS–total scale
1st week				
HDL	r = – 0.530** p = 0.006	r = – 0.466* p = 0.019		r = – 0.507** p = 0.010
CRP	r = 0.527**a p = 0.007	r = 0.597** p = 0.002	r = 0.444* p = 0.026	r = 0.523** p = 0.007
3rd month				
NO_2^-			r = – 0.477* p = 0.016	r = – 0.455* p = 0.022
Chlorpromazine3			r = 0.507** p = 0.010	r = 0.403* p = 0.046

The level of statistical significance was $p < 0.05$ and marked as *

*$p < 0.05$; **$p < 0.01$; **a $p < 0.001$

Discussion

In this pilot study involving a group of young patients with FEP, we demonstrated that an improvement in the clinical symptoms of acute psychosis, as evidenced by the PANNS scores, was associated with a decrease in plasma NO_2^- concentrations, a deterioration in the lipid profile and activation of systemic inflammation. These results point out that early clinical improvement of FEP in young people with no significant metabolic or other risk factors for cardiovascular diseases was not associated with improvement, but surprisingly, with the deterioration of the lipid profile and the activation of systemic inflammation, as well as deterioration of the NO-dependent endothelial function. Taken together, our results suggest that adverse metabolic response, systemic inflammation and a fall in systemic NO bioavailability represent an early systemic manifestation of FEP that are not controlled by short-term antipsychotic treatment and may pose cardiovascular risk.

In our study, the early phase of FEP was clearly associated with the activation of systemic inflammation, as determined by the level of CRP which is produced in response to the action of pro-inflammatory cytokines. A number of previous studies showed the inflammatory changes during the treatment of the first psychotic episode. Dahan et al. [26] showed an increase in the plasma concentration of inflammatory cytokines—namely, interleukin IL-6, IL-2R and IL-8—in a group of 41 patients diagnosed with schizophrenia over the course of psychotic decompensation as compared to the control group. Elsewhere, Noto et al. [27] described the relationship between IL-6

and IL-8 levels and clinical symptoms in a group of 31 patients diagnosed with FEP, whereas Balõtšev et al. [28] underlined the role of IL-1α, IL-6, and tumour necrosis factor alpha (TNF-α) in the psychotic process. In these reports, it was shown that the clinical symptoms of psychosis were proportional to the severity of inflammation, and the clinical improvement was generally associated with the suppression of inflammation. However, the decrease was not observed for all pro-inflammatory cytokines. Luo et al. [29] showed that following the initiation of treatment in 68 patients with schizophrenia, the concentration of IL-6 decreased, while that of IL-18 and TNF-α remained unchanged, suggesting a persisting systemic inflammation in patients at discharge, despite the antipsychotic treatment administered for 68.85 ± 45.66 days. The last studies seem compatible with our results, and underscore a possible dissociation between the effects of antipsychotic treatment and systemic inflammation in patients with psychosis.

Regarding changes in the lipid profile, we reported an increase in TC, LDL, and TG levels and a decrease in HDL level in young patients with FEP, and these changes were significant within 3 months after the admission to the hospital. This observation is in accordance with the literature data indicating that FEP is accompanied by lipid concentration changes. Leppik et al. [30] showed that among the untreated patients with FEP, there was an increase in the levels of lysophosphatidylcholines (LysoPCs) and a significant reduction in phosphatidylcholines (PCs) and sphingomyelins (SMs) when compared to the control group. In a recent meta-analysis, Misiak et al. demonstrated the presence of metabolic dysregulation in patients previously untreated with antipsychotics, with the first episode of non-affective psychosis (FENP). It was found that patients in the early phase of schizophrenia spectrum disorders show specific lipid disorders with both anti-atherogenic (low TC and LDL) and atherogenic features (low HDL and high TG) [31]. On the other hand, Olszewska and Rybakowski [32] observed that the initial stage of treatment of schizophrenia exacerbation was associated with metabolic disorders, which were expressed by an increase in body weight, glucose concentration and TC.

The important finding of this work, differentiating our study from previous studies, was that adverse metabolic response, as well as systemic inflammation were associated with a fall in systemic NO bioavailability. All these features seem to represent early systemic manifestations of FEP that clearly were not controlled by short-term antipsychotic treatment. Of note, the deterioration of the lipid profile, systemic inflammation, and the increase of pro-inflammatory cytokines (e.g., IL-1, IL-6, IL-8, TNF-α) could contribute to the development of endothelial dysfunction in FEP patients [33], but a direct link between FEP and peripheral endothelial dysfunction cannot be excluded [5].

Indeed, systemic inflammation and worsening of the lipid profile in the early phase of acute psychosis, especially in young untreated FEP patients [34], may be a manifestation of an acute onset of psychotic decompensation itself. In agreement with this notion, we found that the duration of untreated psychosis was correlated with a fall in plasma NO_2^- concentrations, which suggests that the development of

systemic vascular endothelial dysfunction occurred before the initiation of treatment. On the other hand, antipsychotic treatment could also contribute to this phenomenon. In fact, as literature data suggests, some antipsychotic drugs (e.g. risperidone) given to diabetic rats promoted an increased level of adhesion molecules (ICAM-1, VCAM-1, E-selectin) and cytokines (MCP-1, TNF-a) [35]. Antipsychotic treatment in patients also led to an increased plasma level of soluble TNF-1 receptor (sTNF-R1), vWf, and high-sensitivity CRP (hs-CRP) [36]. Moreover, antipsychotic treatment was shown to unfavourably affect the lipid profile [37, 38], with differences observed between the individual agents. For example, aripiprazole had a more favourable effect on metabolic parameters than did clozapine, olanzapine, or risperidone [39].

The study has a number of important limitations. It is based on a small study group. Patients' age varied. Only one clinical scale (PANSS) was used to assess symptom severity and clinical improvement. There was no control group involved in the analysis presented in the paper. The studied parameters are potentially influenced by many factors, such as the drugs used or diet. We did not assess endothelial function using FMD or other methodologies that assess the endothelial function [40].

Nevertheless, our results suggest that improvement of clinical symptoms in the course of antipsychotic treatment in patients with the first episode of schizophrenia is accompanied by a decrease in the systemic bioavailability of nitric oxide, as well as inflammatory characteristics and a deterioration of the lipid profile.

Further studies are warranted to better understand the relationship between acute FEP and its consequences for cardiovascular risk and to choose the best option of prevention and treatment. This might be especially important among young patients who might be particularly vulnerable to peripheral manifestations of the acute and severe FEPs, including the unfavourable changes in lipid profile, systemic inflammation, and a decrease in NO bioavailability.

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