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Latent *Toxoplasma Gondii* infection is associated with decreased serum triglyceride to high-density lipoprotein cholesterol ratio in male patients with schizophrenia

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Abstract

Background: Previous studies suggested a complex association between *Toxoplasma Gondii* (TG) infection and host lipid metabolism. Both TG infection and metabolic disturbances are very common in patients with schizophrenia, but this relationship is not clear.

Methods: In this cross-sectional study, we evaluated the association between TG seropositivity, serum lipid levels, body mass index (BMI) and metabolic syndrome (MetS) in 210 male inpatients with schizophrenia.

Results: In our sample of schizophrenia patients, with the mean age of 43.90 ± 12.70 years, the rate of TG seropositivity was 52.38% and the prevalence of MetS was 17%. Patients with the TG antibodies had lower serum triglyceride levels and body weight compared to TG seronegative patients, despite having more frequently received antipsychotics (clozapine, olanzapine risperidone and quetiapine), which are well known to induce weight gain and metabolic abnormalities. However, the only significant change in metabolic parameters, observed in TG seropositive patients with schizophrenia, was decreased serum triglyceride to high-density lipoprotein cholesterol (HDL-C) ratio. No associations were observed between TG seropositivity and serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and glucose levels, waist circumference, BMI and the rate of MetS.

Conclusion: This is the first report of the association between TG infection and decreased serum triglyceride to HDL-C ratio in a sample of carefully selected men with chronic schizophrenia.

Key words: *Toxoplasma Gondii* infection; schizophrenia patients; serum lipid indices; body mass index; metabolic syndrome

1. Introduction

Latent infection with *Toxoplasma Gondii* (TG) has recently raised significant interest in psychiatry, particularly in patients with schizophrenia [1,2]. Schizophrenia is a devastating disorder, which was consistently associated with increased rates of TG infection [2], but also with dyslipidemia [3,4]. Preclinical studies have reported a complex association between TG infection and host lipid metabolism. The parasite accumulates lipids from the host low-density lipoprotein cholesterol (LDL-C) [5]. Given that, TG is unable to synthesize cholesterol; its growth is dependent on the external cholesterol sources. Consequently, infection with TG decreased serum total cholesterol (TC) concentration in apolipoprotein E-deficient mice [6], LDL-C receptor knockout mice fed with hypercholesterolemic diet [5] and in wild-type mice [7]. In general, TG infection reduced serum TC levels in animal models due to its increased uptake [6].

In spite of such profound effects of TG on lipids in animal models, only two studies have investigated lipid levels in human subjects with evidence of TG infection. One study found no difference in serum TC levels from cord blood samples between TG seropositive and seronegative pregnant women [8]. Another study reported a correlation between TG seropositivity and serum TC and LDL-C levels in men with schizophrenia [9]. However, the latter study provided no data on other factors, which affect serum lipid levels in patients, like antipsychotics [4,10], lipid-lowering-agents and severity of symptoms.

Therefore, the link between the TG seropositivity, serum lipid levels and weight is poorly understood in patients with schizophrenia. In addition, there is no data on the relationship between TG infection and metabolic syndrome (MetS), neither in healthy individuals nor in psychiatric patients.

The aim of this study was to investigate the association between TG seropositivity, serum lipid indices, body mass index (BMI) and MetS in men with schizophrenia.

2. Materials and methods

2.1.Subjects and clinical evaluation

This cross-sectional study was conducted at University Hospital Centre Zagreb, Department of Psychiatry, and Psychiatric Hospital Popovaca. Inclusion criteria were: male inpatients aged 18 to 65 years, diagnosed with schizophrenia for at least 5 years. Diagnosis of schizophrenia was confirmed using the Structured Clinical Interview (SCID) [11]. Exclusion criteria were: intellectual disability, patients with first-episode psychosis and/or no previous treatment with antipsychotics, substance abuse and dependence in the previous year, any comorbid severe somatic or neurological disorder, including inherited dyslipidemia and current infection, treatment with lipid-lowering, antidiabetic and /or antihypertensive agents and the use of antidepressants in previous three months.

Only male patients were enrolled in the study in order to exclude the influence of gender on the results. Notably, gender differences were reported in metabolic issues, such as obesity [12], lipid levels [13], the prevalence of MetS [14], and treatment-outcome [15] in patients with schizophrenia. Patients were evaluated using structured interview for the Positive and Negative Symptom Scale (PANSS) [16], including the PANSS positive, negative, general psychopathology and cognitive (PANSS-COGN) subscale (consisting of P2, N5, N7, G7, G10, G11, G12, G14 and G15 PANSS items), as well as with Calgary Depression Scale for Schizophrenia (CDSS) [17] and International Suicide Prevention Trial (InterSePT) Scale [18].

At the time of the assessment, psychiatrists were not aware of the laboratory test results. The study was approved by the local Ethics Committees and was carried out in accordance with the Helsinki declaration (1975). All patients have signed approved informed consent prior to study procedures.

2.2.Determination of TG IgG antibodies

TG immunoglobulin G (IgG) antibodies in serum were determined using VIDAS Toxo IgG test produced by Biomerieux, France. Vidas Toxo IgG is an automated quantitative test for use on the VIDAS family instruments for the quantitative measurement of anti-TG IgG in human serum or plasma using ELFA (Enzyme-Linked-Fluorescent Assay) technique. The assay combines a two-step enzyme immunoassay sandwich method with a final fluorescent detection at 450 nm. Once the assay is completed, the results are analysed automatically by the instrument using calibration curves, which are stored and expressed in international units (IU)/ml. The cut off values are determined by the test kit manufacturer. It has been considered that results up to 4 IU/ml were negative, results from 4 IU/ml to 8 IU/ml were considered equivocal, and results above 8 IU/ml were considered positive.

2.3.Determination of biochemical and anthropometric parameters

Waist and hip circumference (cm), height (cm), and body mass (kg) were measured by hospital nursing stuff. The height and weight were recorded in standing position, barefoot, and in light clothes. Body mass index (BMI) was calculated as body weight in kilograms divided with squared height value in metres. Waist circumference was measured at minimal respiration at the high point of the iliac crest and at the level of the umbilicus.

Venepuncture was performed between 7 and 9 a.m., after 12 h overnight fast. Immediately after collecting, blood samples were transferred to the Department for Laboratory Medicine, University Hospital Centre Zagreb. Serum levels of triglycerides, TC, LDL-C, high-density lipoprotein cholesterol (HDL-C) and glucose were determined on Roche Cobas C501 Chemistry Analyzer. Serum glucose level was determined by enzymatic UV test with hexokinase. LDL-C was calculated using the Friedewald equation. If serum triglyceride concentration exceeded 4.52 mmol/L, LDL-C was estimated by homogeneous enzymatic

colorimetric test with cholesterol oxidase. LDL-C/HDL-C, TC/HDL-C and triglycerides/HDL-C ratios have been also calculated.

MetS definition was used according to NCEP ATP III criteria [19], which requires the presence of three or more of the following criteria: 1) abdominal obesity (waist circumference >102 cm in men); 2) hypertriglyceridemia (≥ 1.7 mmol/l); 3) low HDL-cholesterol (< 1.04 mmol/l in men); 4) high blood pressure (≥ 135/85 mm Hg); 5) high fasting glucose (≥ 6.1 mmol/l).

2.4.Statistical analysis

Statistical analyses were performed with GraphPad Prism version 4.00 (GraphPad Software, San Diego, CA, USA) and MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium).

Normality of data distribution was assessed with the D'Agostino-Pearson omnibus normality test. The differences in the age, the scores on the PANSS total, positive, negative, cognitive and general psychopathology subscales, CDSS and InterSePT total scores, dose of antipsychotics expressed as chlorpromazine equivalent, glucose, TC, HDL-C, LDL-C and triglyceride levels in the blood, LDL-C/HDL-C, TC/HDL-C and triglycerides/HDL-C ratios, as well as the differences in the waist and hip circumference, body weight, and BMI (all expressed as mean ± SD), between TG seropositive and TG seronegative group were analysed by Student t-test (when data showed normal distribution) or by Mann-Whitney test (when normality of the data failed).

The frequencies of smoking, current treatment with clozapine or olanzapine or risperidone or quetiapine, as well as MetS, between different groups of patients with schizophrenia were evaluated by a $\chi 2$-test of independence.

G*Power 3 Software was used for conducting power analyses, i.e. to determine a priori sample size and power. For Mann-Whitney test (with α=0.05; power (1−β)=0.80; median effect size=0.35), total desired sample size was 210, and the actual sample size was 210. For Student t-test (with α=0.05; power (1−β)=0.80; median effect size=0.35), total desired sample size was 204, and the actual sample size was 210. For analyses with a χ2-test (with α=0.05; power (1−β)=0.80 and small effect size (ω=0.20; df =1), total desired sample size was 197, while the actual total sample size was 210. Therefore, power analysis revealed that the study included appropriate sample size and statistical power to detect significant differences.

The results obtained by investigating various demographic and clinical data in TG seropositive and TG seronegative schizophrenia patients (Table 1) were corrected for multiple testing (11 tests) using Bonferroni correction, and the p-value was set to 0.0045. Bonferroni correction for multiple testing was also applied to the results obtained by comparing different metabolic parameters (13 tests) between TG seropositive and TG seronegative group of patients with schizophrenia (Table 2) and the p-value for these data was set to 0.00385.

Finally, multiple regression analysis (Table 3, Supplementary Table) was performed in order to assess the influence of various demographic and clinical data (independent variables), listed in the Table 1, on the 13 different metabolic parameters (dependent variables), listed in the Table 2, in TG seropositive and TG seronegative patients with schizophrenia, and the p-value for these analysis was set to 0.00385.

3. Results

The study enrolled 210 male patients, with the mean age of 43.90 ± 12.70 years. The rate of TG seropositivity in the entire sample of our patients was 52.38% (110/210), which is higher compared to data from the same geographical region, such as 29.10% in healthy Croatian women [20] and 36.40% in the general population from southern Croatia [21]. This finding

supports the compelling evidence, that despite huge differences in TG seroprevalences across countries [22], patients with schizophrenia consistently have higher rates of TG seropositivity than subjects from the appropriate general population [23-26].

Demographic and clinical features of TG seropositive and TG seronegative patients are presented in Table 1. Patients with TG antibodies were significantly older ($p<0.0001$, Mann-Whitney test). As presented in Table 1, TG seropositive and TG seronegative patients did not differ significantly in the number of PANSS total, positive, negative and general psychopathology scores and frequency of smoking. TG seropositive patients had nominally significantly higher number of InterSePT total scores ($p=0.0462$; Mann-Whitney test), and CDSS total scores ($p=0.0148$; Mann-Whitney test), when compared to TG seronegative patients.

Regarding antipsychotic treatment, TG seropositive and TG seronegative patients did not differ significantly in total current dose of antipsychotics, expressed as chlorpromazine equivalent, but TG seropositive group more often received clozapine, olanzapine, risperidone or quetiapine ($p=0.0099$; $\chi 2$ –test), antipsychotics which were the most commonly associated with metabolic abnormalities [19] (Table 1). However, except for age, all other nominally significant results have not survived the multiple testing corrections.

As presented in Table 2, TG seropositive patients had nominally significantly higher HDL-C levels ($p=0.0111$; Student t-test), nominally significantly lower triglycerides levels ($p=0.0193$; Mann-Whitney test), as well as significantly lower triglycerides to HDL-C ratio **($p=0.0019$;** Mann-Whitney test). Patients with the presence of TG antibodies also had significantly lower hip circumference ($p=0.0037$; Mann-Whitney test) and nominally significantly lower body weight ($p=0.0354$; Student t-test). Blood glucose, TC and LDL-C levels, as well as LDL-C to HDL-C ratio, TC to HDL-C ratio, waist circumference and BMI did not differ between TG seropositive and TG seronegative patients (Table 2). The prevalence

of MetS among patients was 17.14 % (36/210), but the distribution of MetS was similar in TG seropositive and TG seronegative groups (p=0.4960; χ2–test).

As shown in Table 3 and Supplementary Table, multiple regression analysis demonstrated nominally significant influence of TG seropositivity on triglyceride levels (p=0.0289), hip circumference (p=0.0148), as well as on the body weight (p=0.0222). In addition to TG infection, multiple regression analysis revealed dose of antipsychotics, expressed as chlorpromazine equivalent, as one of the major variables nominally influencing the triglyceride to HDL-C ratio (p=0.0483), but significantly affecting waist circumference (p=0.0015), hip circumference (p=0.0007), body weight (p<0.0001) and BMI (p=0.0004) (Table 3, Supplementary Table). Moreover, multiple regression analysis (Table 3, Supplementary Table) identified that current treatment with clozapine, olanzapine, risperidone or quetiapine nominally influenced LDL-C levels (p=0.0468); CDSS total scores were significantly associated with triglyceride levels (p=0.0021) and nominally associated with waist circumference (p=0.0492); whereas smoking status nominally affected hip circumference (p=0.0194).

4. Discussion

The main finding of the present study is that TG seropositive patients with schizophrenia had significantly lower triglyceride to HDL-C ratio compared to TG seronegative patients. Differences between TG seropositive and TG seronegative patients with schizophrenia, determined in many other metabolic parameters, such as HDL-C and triglycerides levels, as well as body weight, were only nominally significant, i.e. have not survived the Bonferonni correction for multiple testing.

4.1.TG seropositivity and serum lipid levels

The only study that addressed so far serum lipid levels in patients with schizophrenia according to TG status, has reported increased concentrations of serum TC and LDL-C in TG infected men, and no differences in any lipid indices in women with schizophrenia [9]. The discrepancies [9, present study] might be attributed to types of antipsychotics, diet habits, physical activity and lower number of male participants in the aforementioned study [9] compared to our study (79 vs 210, respectively).

Antipsychotics markedly differ in their propensities to affect serum triglyceride levels. In animal models, olanzapine has elevated serum triglyceride levels [27], whereas haloperidol [28] and aripiprazole [27,28] induced no changes. In first-episode patients, olanzapine has also increased serum triglycerides [4,10], TC and LDL-C levels [10], while risperidone elevated serum TC and LDL-C levels [10]. In our sample, TG seropositive patients more frequently received antipsychotics with higher risk of hyperlipidemia such as clozapine, olanzapine, risperidone and quetiapine [29]. In contrast to Pearce et al. [30], who demonstrated that TG seroprevalence is not elevated in unipolar mood disorders, in our study TG seropositive patients had nominally higher depression scores. Given that second-generation antipsychotics, such as olanzapine, quetiapine and clozapine [31], are slightly more effective in treating depressive symptoms in patients with schizophrenia, the attending psychiatrists might have prescribed those drugs in order to alleviate symptoms of depression.

On the other hand, despite higher prescription of antipsychotics with increased risk of hyperlipidemia, TG seropositive patients in our study had lower triglyceride levels, compared to TG seronegative patients. Although nominally significant, this finding might be of clinical significance; given that our TG seropositive patients had serum triglyceride levels below, while TG seronegative patients had triglyceride levels above the recommended limit of 1.7 mmol/l [19].

Since, in addition to lower triglyceride levels, TG seropositive patients in our study also had nominally higher HDL-C levels, it is not surprising that their triglyceride to HDL-C ratio was significantly lower in comparison to TG seronegative group. Although previous study has not found an association of HDL-C levels with TG seropositivity in patients with schizophrenia [9], this is the first report on TG/HDL-C ratio according to TG status. As high triglyceride to HDL-C ratio was positively associated with metabolic syndrome, insulin resistance and dyslipidemia in general population [32] and patients with schizophrenia [33], likelihood of carotid plaques in postmenopausal women [34], adverse cardiovascular outcomes in general population [35], as well as with cardiovascular disease mortality in men [36], TG seropositive patients appear to have more favorable lipid profile. The triglyceride/HDL ratio has been also shown as useful surrogate to identify subjects with more atherogenic small LDL particles in non-diabetic patients with schizophrenia [33]. However, although infection with TG was found to have complex influence on atherosclerosis [6], our study has not investigated atherosclerosis. Given the utmost importance of atherosclerosis in modern world, it remains to be determined if and how TG infection affects the development of atherosclerosis in schizophrenia.

There is also evidence linking TG infection to suicidality, although the exact mechanisms are not clear [37]. Subjects with recent suicide attempt had lower triglyceride levels compared to patients who did not attempt suicide [38]. Our TG seropositive patients had nominally higher current suicidality, as reflected in their increased InterSePT scores. As clozapine is shown to reduce suicidal behavior in patients with schizophrenia [39], and so far is the only antipsychotic registered by both FDA and EMA for the reduction of the risk for suicidal behavior, this might be the explanation for more frequent clozapine treatment among TG seropositive patients. However, multiple regression analysis confirmed only significant association between CDSS total scores (measuring depression) and triglyceride levels.

Patients with schizophrenia also have poor diet habits. However, all our inpatients received similar, standardized hospital diet. Physical activity could reduce triglyceride levels in patients with schizophrenia [40]. Although patients with schizophrenia have sedentary lifestyle, it cannot be excluded that TG seropositive patients in the current study were more physically active than TG seronegative patients. Notably, TG infection was found to increase activity levels in infected compared to non-infected rats [41] and more recent study has reported elevated open field activity in mice infected with TG [42].

4.2.TG seropositivity and weight

Patients in TG seropositive group had nominally lower body weight compared to seronegative patients. Lower body weight was reported in TG seropositive pregnant women compared to seronegative women [43]. These findings might suggest that TG infection decreases appetite and/or increases activity. Animal data also revealed decreased body weight during TG infection [5]. Decreased appetite was reported in animals [44] and in 83.3% of hospitalized subjects [45] acutely infected with TG, but it is unknown whether TG infection decreases appetite of patients with schizophrenia. Lower body weight in TG seropositive patients could be another reason for prescribing metabolically active antipsychotics in this population, i.e., psychiatrists might have been less reluctant to give such drugs to patients with lower weight.

4.3.TG seropositivity and MetS

The prevalence of MetS of 17 % in our entire sample was unusually low compared to other patients with schizophrenia [3], particularly those treated with clozapine (51.9 %), olanzapine (28.2 %) and risperidone (27.9 %) [3].

Given that age, duration of the disease and treatment with antipsychotics increase the chances of having MetS [3], our patients were even more prone for MetS. The low prevalence of MetS observed in our sample might be related to narrow inclusion criteria.

4.4.Study limitations and strengths

This study is limited by cross-sectional design which precludes any causal assessments. Data on physical activity, appetite and eating habits were not collected. Concentrations of antipsychotics were not determined. Our findings might not be generalizable to women with schizophrenia, first-episode patients, drug-naïve patients, outpatients who are in stable condition and those with significant medical comorbidities.

Most results in our study were only nominally significant i.e. have not survived Bonferonni correction for multiple testing. However, it should be noted that the Bonferroni correction can be conservative if there are a large number of tests and/or the test statistics are positively correlated. Therefore, the Bonferonni correction might increase the probability of producing false negatives, i.e., reducing statistical power. On the other hand, the study has several strengths such as the inclusion of carefully selected, ethnically homogenous Caucasian group of male chronic inpatients with schizophrenia. All patients were evaluated by the same rater. The study had adequate statistical power and sample size.

5. Conclusions

Data presented here suggest that TG seropositive male inpatients with chronic schizophrenia, in spite of being older and receiving more often antipsychotics known to induce metabolic adverse events, have lower triglyceride levels and body weight, compared to TG seronegative patients. However, the only significant change in metabolic parameters, observed in TG seropositive patients with schizophrenia, was decreased serum triglyceride to HDL-C

ratio. Due to the cross-sectional design, it is not possible to conclude if TG infection directly influenced these metabolic parameters due to host-parasite interaction, or just affected drug-compliance, appetite, food intake and physical activity. Future studies are needed to determine whether TG infection relates to more favorable metabolic profile in patients with schizophrenia.

Conflicts of interest

The authors declare that they have no conflict of interests.

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Table 1. Demographic and clinical data of patients with schizophrenia subdivided into TG seropositive and TG seronegative groups

	TG seropositive group (N=110)	TG seronegative group (N=100)	
Mean age (years) (mean ± SD)	48.49 ± 11.90	39.72 ± 11.99	t=5.314; df=208; P<0.0001; Student t-test
Smoking N (%)	74 (67.27)	68 (68.00)	χ^2= 0.01265; df=1; P= 0.9104; χ^2-test
PANSS total score (mean ± SD)	107.50 ± 16.99	110.30 ± 18.10	U=5010; P=0.2659; Mann-Whitney test
PANSS positive score (mean ± SD)	24.02 ± 5.53	25.11 ± 6.78	U=5076; P=0.3351; Mann-Whitney test
PANSS negative score (mean ± SD)	29.42 ± 5.67	30.02 ± 5.88	U=5201; P=0.4962; Mann-Whitney test
PANSS general psychopathology score (mean ± SD)	55.22 ± 8.35	55.47 ± 9.45	U=5437; P=0.8857; Mann-Whitney test
PANSS-COGN score (mean ± SD)	36.43 ± 5.65	35.82 ± 6.24	U=5100; P=0.3627; Mann-Whitney test
CDSS total score (mean ± SD)	7.82 ± 4.50	6.30 ± 3.84	U=4435; P=0.0148 Mann-Whitney test
InterSePT total score (mean ± SD)	3.99 ± 3.88	2.80 ± 2.76	U=4634; P=0.0462 Mann-Whitney test
Dose of antipsychotics (chlorpromazine equivalent) (mean ± SD)	877.2 ± 313.0	863.6 ± 422.1	t=0.2651; df=208; P=0.7912; Student t-test
Current treatment with clozapine/olanzapine/ risperidone/quetiapine N (%)	87 (79.09)	63 (63.00)	χ2=6.646; df=1; P=0.0099; χ2-test

CDSS: Calgary Depression Scale for Schizophrenia; InterSePT: International Suicide Prevention Trial; Scale N: number of subjects; PANSS: Positive and Negative Symptom Scale; PANSS-COGN: PANSS cognitive subscale; SD: standard deviation; TG: *Toxoplasma gondii*.

Table 2. Metabolic parameters of patients with schizophrenia subdivided into TG seropositive and TG seronegative groups

	TG seropositive group (N=110)	TG seronegative group (N=100)	
Glucose (mmol/L) (mean ± SD)	5.303 ± 1.160	5.288 ± 1.077	U=5224; P=0.5302; Mann-Whitney test
LDL-C (mmol/L) (mean ± SD)	2.875 ± 0.9295	2.973 ± 2.207	U=5196; P=0.4894; Mann-Whitney test
HDL-C (mmol/L) (mean ± SD)	1.166 ± 0.4014	1.029 ± 0.3729	t=2.562; df=208; P=0.0111; Student t-test
LDL-C/HDL-C (mean ± SD)	2.722 ± 1.278	3.812 ± 7.444	U=4739; P=0.0836; Mann-Whitney test
TC (mmol/L) (mean ± SD)	4.720 ± 1.069	4.587 ± 1.266	t=0.8249; df=208; P=0.4104; Student t-test
TC/HDL-C (mean ± SD)	4.392 ± 1.584	5.692 ± 9.474	U=4768; P=0.0960; Mann-Whitney test
Triglycerides (mmol/L) (mean ± SD)	1.605 ± 0.9535	1.809 ± 1.004	U=4471; P=0.0193; Mann-Whitney test
Triglycerides/HDL-C (mean ± SD)	1.597 ± 1.262	2.206 ± 2.842	U=4144; P=0.0019; Mann-Whitney test
Waist circumference (cm) (mean ± SD)	95.47 ± 14.59	97.49 ± 11.21	t=1.115; df=208; P=0.2661; Student t-test
Hip circumference (cm) (mean ± SD)	101.3 ± 13.16	105.5 ± 10.82	U=4221; P=0.0037; Mann-Whitney test
Body weight (kg) (mean ± SD)	80.25 ± 14.61	84.75 ± 16.22	t=2.117; df=208; P=0.0354; Student t-test
BMI (kg/m^2) (mean ± SD)	25.86 ± 4.070	26.38 ± 4.467	t=0.8896; df=208; P=0.3747; Student t-test
MetS N (%)	17 (15.45)	19 (19.00)	χ^2=0.4636; df=1; P=0.4960; χ^2–test

BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; N: number; SD: standard deviation; TC: total cholesterol; TG: *Toxoplasma Gondii.*

Table 3. The results (p values) of multiple regression analysis assessing the influence of various demographic and clinical data (independent variables) on the individual metabolic parameters (dependent variables) in patients with schizophrenia. Complete statistical data is presented in Supplementary Table.

	DEPENDENT VARIABLES												
INDEPENDENT VARIABLES	**Glucose**	**LDL-C**	**HDL-C**	**LDL-C /HDL-C**	**TC**	**TC /HDL-C**	**Triglycerides**	**Triglycerides /HDL-C**	**Waist circumference**	**Hip circumference**	**Body weight**	**BMI**	**MetS**
Mean age	0.0723	0.7131	0.0833	0.3969	0.2277	0.3782	0.9045	0.0668	0.1748	0.2629	0.1633	0.8313	0.8188
Smoking	0.0989	0.1210	0.1014	0.2322	0.3233	0.3450	0.9694	0.5040	0.2456	0.0194	0.8475	0.9034	0.8786
TG seropositivity	0.0733	0.1983	0.5984	0.2569	0.2364	0.3095	0.0289	0.0964	0.1079	0.0148	0.0222	0.2223	0.4632
PANSS total score	0.6307	0.6888	0.9632	0.8565	0.5226	0.9672	0.4521	0.3457	0.7541	0.7705	0.6138	0.6781	0.2359
PANSS positive score	0.8115	0.4988	0.4184	0.9132	0.6739	0.6929	0.7011	0.2101	0.9840	0.9896	0.5193	0.6682	0.7540
PANSS negative score	0.2468	0.4671	0.5175	0.7323	0.2653	0.6313	0.1524	0.4618	0.3407	0.7538	0.7160	0.8835	0.0846
PANSS general psychopathology score	0.6183	0.9256	0.7775	0.5189	0.4902	0.5037	0.1338	0.7300	0.2185	0.7813	0.5065	0.5254	0.3120
PANSS-COGN score	0.5792	0.3027	0.4722	0.3165	0.9260	0.4005	0.3852	0.8895	0.5940	0.7855	0.7991	0.6209	0.7770
CDSS total score	0.2151	0.8437	0.1158	0.6931	0.0615	0.9905	0.0021	0.3354	0.0492	0.2166	0.1348	0.2415	0.4547
InterSePT total score	0.3946	0.6758	0.1524	0.9840	0.2132	0.9834	0.0734	0.7599	0.2285	0.2268	0.5351	0.6706	0.6314
Dose of antipsychotics (chlorpromazine equivalent)	0.3175	0.1822	0.7689	0.2096	0.1732	0.2345	0.0519	0.0483	0.0015	0.0007	<0.0001	0.0004	0.1284
Current treatment with clozapine/ olanzapine/ risperidone/ quetiapine	0.5286	0.0468	0.7760	0.1645	0.2113	0.2381	0.0935	0.0951	0.3651	0.1503	0.9614	0.9819	0.7320

BMI: body mass index; CDSS: Calgary Depression Scale for Schizophrenia; HDL-C: high-density lipoprotein cholesterol; InterSePT: International Suicide Prevention Trial Scale; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; PANSS: Positive and Negative Symptom Scale; PANSS-COGN: PANSS cognitive subscale; TC: total cholesterol; TG: *Toxoplasma gondii.*

Supplementary Table: The results of multiple regression analysis assessing the influence of various demographic and clinical data (independent variables) on the individual metabolic parameters (dependent variables) in patients with schizophrenia.

	DEPENDENT VARIABLES												
INDEPENDENT VARIABLES	**Glucose**	**LDL-C**	**HDL-C**	**LDL-C /HDL-C**	**TC**	**TC /HDL-C**	**Triglycerides**	**Triglycerides /HDL-C**	**Waist circumference**	**Hip circumference**	**Body weight**	**BMI**	**MetS**
Mean age													
P	0.0723	0.7131	0.0833	0.3969	0.2277	0.3782	0.9045	0.0668	0.1748	0.2629	0.1633	0.8313	0.8188
Coefficient	0.0399	0.0044	0.0077	-0.0271	0.0176	-0.0360	-0.0010	-0.0240	0.1059	0.0809	-0.1260	0.0055	0.0005
Std. Error	0.0221	0.0119	0.0044	0.0319	0.0146	0.0408	0.0082	0.0130	0.0778	0.0721	0.0900	0.0256	0.0023
$r_{partial}$	0.1277	0.0263	0.1231	-0.0604	0.0859	-0.0628	-0.0086	-0.1302	0.0966	0.0797	-0.0992	0.0152	0.0163
t	1.8070	0.3680	1.7410	-0.8490	1.2100	-0.8830	-0.1200	-1.8430	1.3620	1.1230	-1.3990	0.2130	0.2290
Smoking													
P	0.0989	0.1210	0.1014	0.2322	0.3233	0.3450	0.9694	0.5040	0.2456	0.0194	0.8475	0.9034	0.8786
Coefficient	-0.8947	-0.4508	-0.1785	-0.9325	-0.3525	-0.9424	-0.0077	-0.2130	-2.2125	-4.1500	0.4233	0.0759	-0.0087
Std. Error	0.5395	0.2895	0.1085	0.7782	0.3559	0.9955	0.2014	0.3181	1.8998	1.7605	2.1989	0.6250	0.0567
$r_{partial}$	-0.1173	-0.1103	-0.1165	-0.0851	-0.0704	-0.0673	-0.0027	-0.0476	-0.0827	-0.1656	0.0137	0.0087	-0.0109
t	-1.6580	-1.5570	-1.6460	-1.1980	-0.9900	-0.9470	-0.0384	-0.6700	-1.1650	-2.3570	0.1930	0.1220	-0.1530
TG seropositivity													
P	0.0733	0.1983	0.5984	0.2569	0.2364	0.3095	0.0289	0.0964	0.1079	0.0148	0.0222	0.2223	0.4632
Coefficient	-0.9990	-0.3842	-0.0588	-0.9099	-0.4347	-1.0429	-0.4558	-0.5465	-3.1550	-4.4522	-4.6593	-0.7867	-0.0429
Std. Error	0.5548	0.2976	0.1115	0.8002	0.3660	1.0236	0.2070	0.3271	1.9534	1.8103	2.0221	0.6426	0.0583
$r_{partial}$	-0.1273	-0.0916	-0.0376	-0.0807	-0.0843	-0.0724	-0.1549	-0.1182	-0.1143	-0.1726	-0.1585	-0.0869	-0.0523
t	-1.8010	-1.2910	-0.5280	-1.1370	-1.1880	-1.0190	-2.2010	-1.6710	-1.6150	-2.4590	-2.3040	-1.2240	-0.7350
PANSS total score													
P	0.6307	0.6888	0.9632	0.8565	0.5226	0.9672	0.4521	0.3457	0.7541	0.7705	0.6138	0.6781	0.2359
Coefficient	0.0300	0.0134	-0.0006	0.0163	0.0263	0.0047	0.0175	-0.0347	0.0688	0.0593	-0.1282	-0.0300	0.0078
Std. Error	0.0622	0.0334	0.0125	0.0898	0.0411	0.1148	0.0232	0.0367	0.2192	0.2031	0.2537	0.0721	0.0065
$r_{partial}$	0.0343	0.0286	-0.0033	0.0129	0.0456	0.0029	0.0536	-0.0672	0.0223	0.0208	-0.0360	-0.0296	0.0844
t	0.4810	0.4010	-0.0461	0.1810	0.6400	0.0412	0.7530	-0.9450	0.3140	0.2920	-0.5050	-0.4160	1.1890
PANSS positive score													
P	0.8115	0.4988	0.4184	0.9132	0.6739	0.6929	0.7011	0.2101	0.9840	0.9896	0.5193	0.6682	0.7540
Coefficient	-0.0188	-0.0286	-0.0128	0.0124	-0.0219	0.0573	-0.0113	0.0583	0.0055	-0.0033	0.2068	0.0391	-0.0026
Std. Error	0.0786	0.0422	0.0158	0.1134	0.0519	0.1450	0.0293	0.0463	0.2767	0.2565	0.3203	0.0910	0.0083
$r_{partial}$	-0.0171	-0.0482	-0.0577	0.0078	-0.0300	0.0282	-0.0274	0.0892	0.0014	-0.0009	0.0460	0.0306	-0.0223
t	-0.2390	-0.6780	-0.8110	0.1090	-0.4210	0.3950	-0.3840	1.2570	0.0200	-0.0130	0.6460	0.4290	-0.3140
PANSS negative score													
P	0.2468	0.4671	0.5175	0.7323	0.2653	0.6313	0.1524	0.4618	0.3407	0.7538	0.7160	0.8835	0.0846
Coefficient	-0.1062	-0.0358	-0.0119	0.0452	-0.0674	0.0811	-0.0490	0.0398	-0.3075	-0.0937	-0.1358	-0.0156	-0.0167
Std. Error	0.0914	0.0491	0.0184	0.1319	0.0603	0.1687	0.0341	0.0539	0.3220	0.2984	0.3727	0.1059	0.0096
$r_{partial}$	-0.0825	-0.0518	-0.0461	0.0244	-0.0793	0.0342	-0.1018	0.0525	-0.0679	-0.0224	-0.0260	-0.0105	-0.1226

t	-1.1620	-0.7290	-0.6480	0.3430	-1.1170	0.4810	-1.4370	0.7370	-0.9550	-0.3140	-0.3640	-0.1470	-1.7330
PANSS general psychopathology score													
P	0.6183	0.9256	0.7775	0.5189	0.4902	0.5037	0.1338	0.7300	0.2185	0.7813	0.5065	0.5254	0.3120
Coefficient	-0.0402	-0.0040	0.0046	-0.0751	-0.0367	-0.0995	-0.0452	-0.0164	-0.3501	-0.0730	-0.2184	-0.0594	-0.0086
Std. Error	0.0805	0.0432	0.0162	0.1162	0.0531	0.1486	0.0301	0.0475	0.2836	0.2628	0.3282	0.0933	0.0085
$r_{partial}$	-0.0355	-0.0067	0.0201	-0.0460	-0.0492	-0.0477	-0.1067	-0.0246	-0.0876	-0.0198	-0.0474	-0.0453	-0.0720
t	-0.4990	-0.0934	0.2830	-0.6460	-0.6910	-0.6700	-1.5060	-0.3460	-1.2340	-0.2780	-0.6650	-0.6360	-1.0140
PANSS-COGN score													
P	0.5792	0.3027	0.4722	0.3165	0.9260	0.4005	0.3852	0.8895	0.5940	0.7855	0.7991	0.6209	0.7770
Coefficient	0.0444	-0.0443	0.0116	-0.1158	-0.0049	-0.1243	0.0260	-0.0066	0.1503	-0.0711	0.0830	0.0459	-0.0024
Std. Error	0.0799	0.0429	0.0161	0.1153	0.0527	0.1475	0.0298	0.0471	0.2815	0.2608	0.3258	0.0926	0.0084
$r_{partial}$	0.0395	-0.0734	0.0512	-0.0714	-0.0066	-0.0599	0.0619	-0.0099	0.0380	-0.0194	0.0182	0.0353	-0.0202
t	0.5550	-1.0330	0.7200	-1.0040	-0.0930	-0.8420	0.8700	-0.1390	0.5340	-0.2730	0.2550	0.4950	-0.2840
CDSS total score													
P	0.2151	0.8437	0.1158	0.6931	0.0615	0.9905	0.0021	0.3354	0.0492	0.2166	0.1348	0.2415	0.4547
Coefficient	0.0945	-0.0081	0.0241	-0.0433	0.0943	0.0017	0.0885	0.0433	0.5298	0.3075	0.4652	0.1035	0.0060
Std. Error	0.0760	0.0408	0.0153	0.1096	0.0502	0.1403	0.0284	0.0448	0.2677	0.2481	0.3098	0.0881	0.0080
$r_{partial}$	0.0883	-0.0141	0.1118	-0.0281	0.1328	0.0008	0.2170	0.0686	0.1396	0.0880	0.1064	0.0834	0.0533
t	1.2440	-0.1970	1.5790	-0.3950	1.8810	0.0119	3.1210	0.9660	1.9790	1.2400	1.5010	1.1750	0.7490
InterSePT total score													
P	0.3946	0.6758	0.1524	0.9840	0.2132	0.9834	0.0734	0.7599	0.2285	0.2268	0.5351	0.6706	0.6314
Coefficient	-0.0732	-0.0193	-0.0248	0.0025	-0.0707	-0.0033	-0.0576	-0.0155	-0.3651	-0.3396	-0.2174	-0.0423	-0.0043
Std. Error	0.0858	0.0461	0.0173	0.1238	0.0566	0.1584	0.0320	0.0506	0.3022	0.2801	0.3498	0.0994	0.0090
$r_{partial}$	-0.0607	-0.0298	-0.1018	0.0014	-0.0886	-0.0018	-0.1272	-0.0218	-0.0858	-0.0861	-0.0442	-0.0303	-0.0342
t	-0.8530	-0.4190	-1.4370	0.0200	-1.2490	-0.0208	-1.8000	-0.3060	-1.2080	-1.2130	-0.6210	-0.4260	-0.4810
Antipsychotic dose (chlorpromazine equivalent)													
P	0.3175	0.1822	0.7689	0.2096	0.1732	0.2345	0.0519	0.0483	0.0015	0.0007	<0.0001	0.0004	0.1284
Coefficient	0.0007	0.0005	0.0001	0.0013	0.0006	0.0015	0.0005	0.0008	0.0080	0.0079	0.01223	0.0029	0.0001
Std. Error	0.0007	0.0004	0.0001	0.0010	0.0005	0.0013	0.0003	0.0004	0.0025	0.0023	0.0029	0.0008	0.0001
$r_{partial}$	0.0712	0.0950	0.0209	0.0893	0.0969	0.0847	0.1380	0.1401	0.2232	0.2394	0.2906	0.2480	0.1081
t	1.0020	1.3390	0.2940	1.2590	1.3670	1.1930	1.9560	1.9870	3.2140	3.4610	4.2630	3.5930	1.5270
Current treatment with clozapine/olanzapine/ risperidone/quetiapine													
P	0.5286	0.0468	0.7760	0.1645	0.2113	0.2381	0.0935	0.0951	0.3651	0.1503	0.9614	0.9819	0.7320
Coefficient	0.3469	0.5899	0.0315	1.1061	0.4547	1.1999	0.3457	0.5435	-1.7567	-2.5899	-0.1086	0.0145	0.0198
Std. Error	0.5496	0.2949	0.1105	0.7927	0.3626	1.0140	0.2051	0.3240	1.9351	1.7933	2.2398	0.6366	0.0578
$r_{partial}$	0.0449	0.1411	0.0203	0.0989	0.0890	0.0840	0.1192	0.1187	-0.0645	-0.1024	-0.0034	0.0016	0.0244
t	0.6310	2.0010	0.2850	1.3950	1.2540	1.1830	1.6850	1.6770	-0.9080	-1.4440	-0.0485	0.0227	0.3430

BMI: body mass index; CDSS: Calgary Depression Scale for Schizophrenia; HDL-C: high-density lipoprotein cholesterol; InterSePT: International Suicide Prevention Trial Scale; LDL-C: low-density lipoprotein cholesterol; MetS: metabolic syndrome; PANSS: Positive and Negative Symptom Scale; PANSS-COGN: PANSS cognitive subscale; TC: total cholesterol; TG: *Toxoplasma gondii.*