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## Serum peroxisome proliferator-activated receptor-gamma levels in acute phase of male patients with schizophrenia and their relationship with metabolic parameters

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### ABSTRACT

**Objective:** Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor family providing the modulation of the genes having a role in gluco-lipid metabolism and inflammation. Here, we aimed to compare serum PPAR $\gamma$  levels between medication-free schizophrenia patients and healthy controls.

**Methods:** Forty-five inpatients with schizophrenia and 39 healthy controls were included in the study. Serum PPAR $\gamma$  levels and metabolic syndrome (MetS) parameters of the patients and controls were compared.

**Results:** There were no statistically significant differences between the patients ( $1.42 \pm 0.64$  ng/ml) and the control group ( $1.59 \pm 1.10$  ng/ml) in terms of serum PPAR $\gamma$  levels. No statistically significant correlations were determined between the MetS parameters and PPAR $\gamma$  levels.

**Conclusions:** Our findings showed that PPAR $\gamma$ , which we predicted to have a role in metabolic disorders and inflammatory process in schizophrenia, did not seem to have a role in the acute exacerbation of schizophrenia.

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### KEYWORDS

Inflammation; metabolic syndrome; PPAR-gamma; schizophrenia

## Introduction

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor protein that function as transcription factors regulating the gene expression. They also have a role in the regulation of cellular differentiation and growth, and carbohydrate, lipid, and protein metabolism. PPARs are activated by fatty acids and their oxidation products [1]. There are three subtypes of PPAR: PPAR  $\alpha$ ,  $\beta$ , and  $\gamma$ . All of those subtypes show structural and functional differences but all three of them have a role primarily in glucose and lipid metabolism and inflammation [2]. PPAR $\gamma$  regulates the expression of a number of genes effective in lipid and glucose metabolism. Also, it acts as a potent anti-inflammatory agent by means of the indirect interaction with transcription factors [3,4]. PPAR $\gamma$  is highly expressed in white adipose tissue and its activation results in the increase of white adipose tissue [5]. Thus, PPAR $\gamma$  is thought as a main regulator in adipogenesis. Furthermore, it was shown that PPAR $\gamma$ , whose expression is less in tissues other than adipose tissue, was shown to regulate the metabolism and inflammation in tissues such as the human brain [6]. The regulatory function of PPAR $\gamma$  on both glucose and lipid metabolism and regulating the inflammation in both the brain and other tissues indicates that this

molecule might be related to the etiology of schizophrenia and the metabolic abnormalities in schizophrenia. In this study, we aimed to compare the serum PPAR $\gamma$  levels in medication-free schizophrenia patients during the acute phase of psychotic episode with those of the healthy control group.

## Methods

### Participants

Schizophrenia patients who were diagnosed according to DSM-IV-TR criteria and who were hospitalized in Bakırköy Mental Health Research and Training Hospital between February 2014 and May 2014 were screened for the study. Inclusion criteria were (1) age between 18 and 65 years and (2) being drug free, at least for one week. Exclusion criteria were (1) alcohol and/or substance dependence or other axis I disorder and (2) having other chronic medical conditions (diabetes mellitus, thyroid diseases, Cushing's disease, and other endocrine disorders) or medication.

Age- and gender-matched healthy individuals were included to the study as the control group. Our study sample only consisted of male patients in order to exclude interference of the possible effects of the female hormones on PPAR $\gamma$ . It was aimed to minimize the

effects of antipsychotic drugs on PPAR $\gamma$  by including only the patients, who stopped using the antipsychotic drugs at least one week before the study participation. The diagnosis was confirmed by at least two clinicians using clinical interviews. Patients with diagnosis of another axis I were excluded.

Forty-five patients were included according to the criteria of the study. A socio-demographical form was filled out and the severity of illness was measured by Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Additionally, 39 age- and gender-matched healthy controls participated in the study. In this study, we evaluated metabolic syndrome (MetS) parameters according to ATP-III criteria including: *waist circumference*, male > 102 cm (>40 in); *blood pressure*, systolic  $\geq$  130 mmHg, diastolic  $\geq$  85 mmHg; *high density lipoprotein (HDL) cholesterol*, male < 40 mg/dL (1.04 mmol/L); *triglycerides (TG)*  $\geq$  150 mg/dL (1.7 mmol/L); and *fasting glucose*  $\geq$  110 mg/dL (6.1 mmol/L).

**Blood sample for PPAR $\gamma$  level:** The blood samples were collected in the morning around 8 a.m. from a forearm vein of the participants at the end of an overnight fasting period for at least 8 h. Tubes with 5 ml capacity were used to collect blood. Then, the blood was carefully and immediately transferred from these tubes to centrifuge tubes. The first tube was stored in ice immediately. After the centrifugation process at 1600 $\times$ g for 15 min at 4°C, the serum was obtained and stored at -80°C until the time of assay. Mybio-source Human proxisome proliferator-activated receptor gamma (PPAR-Gamma) ELISA Kit (Catalog No: #MBS2630B9, Lot Number: 38266232) was used to determine the PPAR $\gamma$  levels in serum samples.

This study was approved by the Ethics Committee of Bakırköy Dr. Sadi Konuk State Hospital (protocol date and number: 27 January 2014 and 2013/134) and all participants or their legal representatives gave written informed consents before the enrollment in the study.

### Statistical analysis

All statistical analyses were performed using SPSS Version 16 for Windows was used for. Descriptive statistical methods (mean, standard deviation, and frequency) were used while analyzing the study data. Student's *t*-test was used for the comparison of data with normal distribution and Mann-Whitney-U test was used in comparison of parameters not normally distributed. After logarithmic transformation of the PPAR $\gamma$  data for normalization, one-way analysis of covariance (ANCOVA) was performed for comparisons between groups after adjustment for age and Body Mass Index (BMI). Chi-square test was used in the comparison of dichotomic data. Pearson and Spearman correlation analyses were used to evaluate the relationship between variables. The alpha level of 0.05 was set up to indicate significance.

### Results

The study samples consisted of 45 patients and 39 healthy control subjects and all of them were male. The mean age of the patient group was  $34.62 \pm 9.37$  years and the mean age of the control group was  $33.17 \pm 7.30$  years. There were no statistically significant differences between patients and control group in terms of age ( $p = .115$ ).

The mean duration of illness was  $9.04 \pm 7.20$  years, the age at illness onset was  $25.70 \pm 8.80$  years, and the first treatment age was  $26.80 \pm 9.10$  years. The mean hospitalization frequency was  $4.30 \pm 4.50$  times. The PANSS score means were  $95.20 \pm 17.97$  (min: 51 and max: 131) and the BPRS scores were  $34.80 \pm 10.10$  (min: 14 and max: 59) during the index hospitalization (Table 1).

No statistically significant differences were detected in terms of PPAR $\gamma$  levels between patients ( $1.42 \pm 0.64$  ng/ml) and the control group ( $1.59 \pm 1.10$  ng/ml) ( $p = .473$ ). When the patient and the control group were compared in terms of MetS parameters: as for fasting blood glucose,  $87.71 \pm 17.73$  mg/dL (median: 85) vs.  $84.16 \pm 7.96$  mg/dL (median: 84) and  $p = .679$ ; for HDL level,  $41.36 \pm 9.03$  mg/dL vs.  $46.88 \pm 13.84$  mg/dL and  $p = .044$ ; for TG level,  $132.70 \pm 90.22$  mg/dL (median: 93.50) vs.  $136.36 \pm 73.76$  mg/dL (median: 104) and  $p = .462$ ; for waist circumference  $92.73 \pm 12.22$  cm vs.  $94.51 \pm 7.79$  cm and  $p = .427$ ; for systolic blood pressure,  $115.78 \pm 6.56$  mm Hg (median: 120) vs.  $107.31 \pm 9.90$  mm Hg (median: 110) and  $p < .001$ ; for diastolic blood pressure  $72.00 \pm 6.60$  mm Hg (median: 70) vs.  $68.37 \pm 7.99$  mm Hg (median: 70) and  $p = .019$  (Table 2).

Number of patients meeting at least three of MetS diagnosis criteria in index evaluation was four (8.8%). Four individuals in control group (10.2%) also met the MetS diagnosis criteria. There were no statistically significant difference between the patient and the control group in terms of the meeting the MetS criteria ( $\chi^2 = 0.045$ , df = 1,  $p = .326$ ).

No statistically significant difference was found when patient and control group were compared in terms of BMI ( $25.54 \pm 4.34$  vs.  $25.63 \pm 2.34$ ,  $p = .908$ ). When the other hematological and biochemical parameters were considered, albumin, potassium, and calcium levels were statistically significantly lower, and

**Table 1.** Demographics and clinical features of study patients.

<i>n</i> = 45	Mean $\pm$ SD	Min-max
Age	$34.62 \pm 9.37$ years	19-57
Disease duration	$9.04 \pm 7.2$ years	1-25
Age of onset	$25.75 \pm 8.8$	13-57
First treatment age	$26.84 \pm 9.01$	13-58
Total hospitalization	$4.33 \pm 4.51$	1-19
PANSS	$95.2 \pm 17.97$	51-131
BPRS	$34.8 \pm 10.1$	14-59

Note: SD: Standard Deviation

**Table 2.** PPAR $\gamma$ , MetS parameters, and other biochemical and hematological parameter levels of patient and control groups.

	Patient (n = 45)	Control (n = 39)	p
PPAR $\gamma$ (ng/ml) <sup>a</sup>	1.42 $\pm$ 0.64	1.59 $\pm$ 1.10	.473
Fasting blood glucose (mg/dL) <sup>a</sup>	0.12 $\pm$ 0.13n	0.15 $\pm$ 0.18n	.679
High density lipoprotein (mg/dL)	85 (78–91)	84 (82–89)	.044*
Triglyceride (mg/dL)	41.36 $\pm$ 9.03	46.88 $\pm$ 13.84	.462
Waist circumference (cm)	93.50 (76.25–165.25)	104 (83–187)	.427
Systolic blood pressure (mm Hg) <sup>a</sup>	92.73 $\pm$ 12.22	94.51 $\pm$ 7.79	<.001**
Diastolic blood pressure (mm Hg) <sup>a</sup>	120 (110–120)	110 (100–110)	.019*
Leukocyte ( $\mu$ L)	70 (70–80)	70 (60–70)	.001**
Hemoglobin (g/dL)	8.71 $\pm$ 2.33	7.18 $\pm$ 1.62	.141
Hematocrit (%)	14.66 $\pm$ 1.46	15.08 $\pm$ 1.05	.279
Platelet ( $\mu$ L)	44.24 $\pm$ 3.92	45.07 $\pm$ 2.97	.219
Sodium (mmol/L)	250.32 $\pm$ 79.40	233.31 $\pm$ 41.46	.052
Potassium (mmol/L)	140.80 $\pm$ 2.02	141.97 $\pm$ 3.04	.040*
Calcium (mg/dL)	4.26 $\pm$ 0.37	4.42 $\pm$ 0.29	<.001**
Albumin (mg/dL)	9.28 $\pm$ 0.46	9.82 $\pm$ 0.27	<.001**
Total cholesterol (mg/dL)	4.30 $\pm$ 0.32	4.61 $\pm$ 0.24	.125
Low density lipoprotein (mg/dL)	178.14 $\pm$ 51.45	192.97 $\pm$ 33.59	.780
Sedimentation (mm/h) <sup>a</sup>	116.44 $\pm$ 59.22	119.26 $\pm$ 27.74	.007**
C-reactive protein (mg/L) <sup>a</sup>	6 (3.5–14)	4 (3–5.5)	<.001**

Note: n, adjusted PPAR $\gamma$  level data for BMI and age with ANCOVA. PPAR $\gamma$ , peroxisome proliferator-activator receptors  $\gamma$ , MetS, metabolic syndrome.

<sup>a</sup>Mann–Whitney U test (shown as median and (25–75%)) and student's *t*-test (shown as mean  $\pm$  standart deviation) were used.

\**p* < .05.

\*\**p* < .001.

leukocyte, aspartate aminotransferase, sedimentation, and C-reactive protein (CRP) levels were statistically significantly higher in patients compared to those in the control group (Table 2).

No statistically significant correlation was found between PPAR $\gamma$  levels and fasting blood glucose ( $r_s = 0.141$ ,  $p = .208$ ), waist circumference ( $r_s = 0.009$ ,  $p = .937$ ), HDL ( $r_s = 0.056$ ,  $p = .625$ ), TG ( $r_s = 0.090$ ,  $p = .428$ ), systolic ( $r_s = 0.083$ ,  $p = .456$ ), and diastolic ( $r_s = 0.009$ ,  $p = .933$ ) blood pressure. No statistically significant correlations were found between the PPAR $\gamma$  levels and the duration of the disease ( $r_s = 0.047$ ,  $p = .759$ ), total hospitalization period ( $r_s = 0.143$ ,  $p = .349$ ), and PANSS ( $r_s = 0.046$ ,  $p = .763$ ) and BPRS ( $r_s = 0.109$ ,  $p = .475$ ) scores.

## Discussion

One of the main findings of our study was that there were no statistically significant differences between the patients and control group in terms of PPAR $\gamma$  levels.

In contrast to many studies about genetic relationship between weight gain in schizophrenia and PPAR $\gamma$ , in the present study we examined the serum level of PPAR $\gamma$  level in patients with schizophrenia. With the hypothesis stating that due to the increased Type 2 diabetes risk in schizophrenia patients, there might be a genetic relationship between those diabetes and schizophrenia, the relationship of this gene with the Type 2 diabetes was found but it was shown that it was not related to the schizophrenia development [7]. Herken et al. detected that there was PPAR $\gamma$  gene polymorphism in schizophrenia patients who were administered olanzapine and who had weight gain in their study [8]. In another clinical study, both PPAR $\gamma$  and PPAR $\gamma$  gene was presented to be related with the weight gain induced by clozapine, similar to

olanzapine, and the MetS [9]. In a study examining the effects of PPAR $\gamma$  agonists on the cognitive functions in schizophrenia patients treated with clozapine, it was shown that PPAR $\gamma$  agonists do not have any positive effects on the cognitive functions [10]. Preclinical studies revealed that rosiglitazone, PPAR $\gamma$  agonist, decreased both the glucose and lipid levels in animals treated with antipsychotics but it did not decrease the insulin levels as fenofibrate [11].

Another result of our study was that there was no statistically significant difference between the patients meeting MetS criteria and the control group. The studies showed that mortality rate was 2- to 3-fold higher in schizophrenia patients when compared to general population. Cardiovascular diseases are seen in an increasing prevalence in this patient group and it is considered as the reason for increasing mortality [12–14]. Therefore, it is important for the clinicians to reveal the cardiovascular risk factors. MetS is a concept in which clinical and metabolic abnormalities, which facilitates the prediction of cardiovascular morbidity risk, are evaluated together [15]. In literature, antipsychotic treatment is blamed among one of the reasons of higher MetS prevalence in schizophrenia patients [16]. In a study involving meta-analysis for evaluating the prevalence of MetS parameters, it was stated that one-fifth of the schizophrenia patients had significant hyperglycemia, more than half of them was overweight, and at least two out of five had lipid abnormalities [17]. In our study, there was no patient with hyperglycemia since the patients with diabetes and metabolic disorder were excluded due to exclusion criteria. Our exclusion criteria appeared to be another reason for that the number of patients who can meet MetS criteria were lower than expected. However, lower HDL levels were found in 44.4% of our patients, higher TG in 26.6% of them, and higher waist



circumference in 24.4% of them, which were consistent with the literature. MetS frequency was compared in first episode, under treatment and medication-free schizophrenia patients in a meta-analysis conducted by Mitchell et al.; a significant difference was found between groups as 35.3% in medication taking group, 9.8% in medication-free group, and 9.9% in the first-episode patients [17]. The finding that the MetS frequency in the first-episode patients was similar to that in the medication-free patients in this meta-analysis provided further support to the contribution of antipsychotics to the development of MetS. The MetS frequency in schizophrenia patients in our study (8.8%) was consistent with the literature.

In our study there were no correlations between the MetS parameters and PPAR $\gamma$  levels. In the literature, it was reported that the weight gain in schizophrenia patients who are using atypical antipsychotics was related to PPAR $\gamma$  gene polymorphism [18] and the glucose-level changes in patients who were administered antipsychotics may have been related to PPAR $\gamma$  gene [19]. Although PPAR $\gamma$  activity was shown to have a role in glucose and lipid metabolisms and Type 2 diabetes, we did not find a relationship between serum PPAR $\gamma$  level and MetS parameters. Excluding patients with higher fasting blood glucose or comorbid diabetes and/or other metabolic disorders or including drug free patients might have led to such negative findings. In a study examining the relationship between PPAR $\gamma$  gene polymorphism and the metabolic disorders in schizophrenia and schizoaffective disorder patients, it was reported that the obesity or MetS seen in schizophrenia patients was not found to be related with the polymorphism of this gene [20]. Similarly, there are also studies in the literature supporting our finding that there were no relationships between PPAR $\gamma$  and metabolic disorders in schizophrenia [11,21].

It was shown that in a number of studies examining the relationship of schizophrenia and inflammation, the inflammatory cytokines were increased in schizophrenia patients compared to the controls. In those studies, it was found that the indicators such as interleukin (IL) 1-beta, IL-6, and transforming growth factor-beta increased during acute inflammation and the indicators such as IL-12, interferon-gamma, and tumor necrosis factor alpha increased during both acute and chronic period compared to control group [22]. Studies showing the protective role of PPAR $\gamma$  agonists in animal studies conducted for neurological diseases such as Alzheimer's disease and multiple sclerosis and the studies displaying that neuro-inflammation was prevented by PPAR $\gamma$  ligands indicated that PPAR $\gamma$  might have had a role in schizophrenia and inflammation relationship [23]. In a study conducted by Martínez-Gras et al., it was indicated that prostaglandin 15d-PGJ 2 (an anti-inflammatory molecule) and its nuclear receptor PPAR $\gamma$  were decreased

in patients with schizophrenia [24]. In the present study, there was a significant difference between patient and control group in terms of inflammation indicators such as CRP, sedimentation, leukocyte number, and albumin levels, while there were no differences in terms of PPAR $\gamma$ . Hence, we considered that PPAR $\gamma$  was not related to possible acute inflammatory response in schizophrenia patients.

The present study has certain limitations. We think that refining our study group by including both medication-free and male patients and by excluding other confounding factors help us to better understand the relationship between the schizophrenia and PPAR $\gamma$ . On the other hand, excluding the patients with metabolic disorders, which can be related to PPAR $\gamma$ , might have resulted in not constituting a sample to represent schizophrenia population. Also criteria for being medication-free for at least one week could be insufficient to eliminate the effects of antipsychotics on PPAR $\gamma$ . This might be considered another limitation of our study. Cross-sectional nature of our study might pose another limitation. It would be more valuable to measure the PPAR $\gamma$  levels of patients after reaching remission phase. Further studies with larger samples which can represent all schizophrenia patients are needed to understand the role of PPAR $\gamma$  in the etiology of schizophrenia and to get a better understanding of its relationship with the remission phases of the illness.

In conclusion, this study showed that PPAR $\gamma$ , which we predicted to have a role in metabolic disorders and inflammatory process in schizophrenia, did not seem to have a role in the acute phase of schizophrenia.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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