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MAY PPAR GAMMA BE SIGNIFICANT IN BIPOLAR DISORDER ONLY IN THE PRESENCE OF METABOLIC SYNDROME?

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Abstract

Background: *Peroxisome proliferator-activated receptor γ (PPARγ) has a key role in regulating both neurogenesis and various metabolic processes, including adipogenesis and glucose homeostasis. In this study, it was aimed to compare the serum PPARγ levels and metabolic syndrome (MetS) parametres of patients with Bipolar Disorder (BD) diagnosed manic-depressive-euthymic episodes with those of healthy subjects.*

Subjects and Methods: *We included 121 male patients with BD type I, 44 in mania, 35 in depression and 42 in euthymic state, and 41 healthy controls. Serum PPARγ levels, inflammation indicators (CRP, neutrophil, leukocyte, and albumin) and Mets parametres were measured.*

Results: *There were no statistically significant differences between the groups in terms of PPARγ values. PPARγ serum level is highest in the control group and then euthymic, manic and depressive episodes continue to decrease, respectively. However, there was a significant difference between the depressive group with MetS and without MetS in terms of serum PPARγ levels. A statistically significant correlation was found between PPARγ and the other serum markers such as low-density lipoprotein (p=0.022), HbA1c (p=0.002), neutrophils levels (0.001), white blood cell (p=0.025), and clinical features such as age at first treatment (p=0.024), age at first episode (p=0.039), and smoking (0.013).*

Conclusions: *We suggest that PPARγ may be a key factor in the BD depressive group with MetS. Not finding any relationship between the PPARγ levels and the episode of BD may be related with the absence of MetS in the individuals. MetS parametres must also be considered if PPARγ is to be evaluated in the future investigations.*

Keywords: *bipolar disorder, metabolic syndrome, PPARγ, depressive episode, inflammation*

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INTRODUCTION

Biological, genetic, or psychological factors have all been exhaustively explored as potential components in the pathogenesis of Bipolar Disorder (BD), but none of these attempts have been able to pinpoint a clear pathophysiological pattern for the illness. Data regarding neurobiological background of BD are expanding rapidly and current evidence supports that various inflammatory processes play a role in the pathophysiology of BD (Çakır et al. 2015, Kalelioglu et al. 2017).

Peroxisome proliferator-activated receptors (PPARs) are a class of ligand-activated transcription factors belonging to the nuclear receptor superfamily. The peroxisome proliferator–activated receptors (PPARs) are a group of three nuclear receptor isoforms encoded by specific genes: PPARγ (PPAR-gamma), PPARα (alpha), and PPARδ (delta) (Khera et al. 2022). PPARγ is a target for insulin sensitizers and plays an essential role in regulating various metabolic processes, including adipogenesis and glucose homeostasis. Moreover, evidence demonstrates that PPARγ has a key role in regulating neurogenesis. PPARγ downregulates pro-inflammatory genes, such as those encoding cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (NOS), and stimulates the production of anti-inflammatory cytokines and chemokines (Kapadia et al. 2008). It has been reported that PPARγ is implicated in macrophage polarization, from a pro-inflammatory and neurotoxic M1 phenotype to an anti-inflammatory and neurotrophic M2 phenotype (Govindarajulu et al 2018). Moreover, PPARγ reduces reactive oxygen species as a secondary messenger in the inflammatory response (Korbecki et al. 2019).

The pharmacological activation of PPARγ using specific ligands increases the proliferation and differentiation of neural stem cells in specific brain regions, including the hippocampus. Beside this, PPARγ agonists prevent neurodegeneration and improve cognition (Lim et al. 2021). The PPARγ agonist rosiglitazone and other synthetic compounds improve anxiety and depression-like behaviors in rodent models (Rosa et al 2008). Pioglitazone shows similar antidepressant effect in animal model, which is antagonized by the presence of a PPARγ antagonist (Sadaghiani et al. 2011). Moreover, recent evidence has reported an interesting relationship between PPARγ activation, depression, and neurogenesis. Neuronal seipin-deficient mice exhibit depression-like behavior and suppressed adult neurogenesis with reduced expression of PPARγ. Rosiglitazone restores the decrease in PPARγ expression and improves depression-like behaviors (Li et al. 2015). In fact, emerging evidence shows that the activation of PPARγ can potentially regulate adult neurogenesis.

PPARγ is found in elevated levels in the brains of individuals with Alzheimer's disease. This type of receptor has a physiological function in modulating inflammatory responses. In animal models of Alzheimer's disease, PPARγ agonist treatment results in the reduction of amyloid plaque burden, reduced inflammation and reversal of disease-related behavioral impairment. The use of the PPARγ agonist rosiglitazone was associated with improved cognition and memory in patients with mild to moderate Alzheimer's disease (Jiang et al. 2008).

PPARγ agonism may play a role in autism treatment by reducing inflammatory cytokine release and microglial activation. The levels of signal transducer activator of transcription (STAT) and PPARγ in rats with autism confirm the involvement of signaling processes in the pathology of autism (Khera et al. 2022). Moreover, activation of PPARγ has a neuroprotective effect by reducing inhibition of the brain-derived neurotrophic factor (BDNF) signaling pathway and serves its function by enhancing learning and memory, neurogenesis, synapse formation. Furthermore, PPARγ agonists regulate the oxidation of free fatty acids and increase ATP, reducing oxidative stress, ROS (reactive oxygen species), and neuroinflammation, and hence neurodegeneration (Khera et al. 2022).

PPARγ is a marker that has been also studied in psychiatric disorders. García-Álvarez et al. reported that there were no differences between patients with schizophrenia and healthy controls in terms of anti-inflammatory parameters containing PPARγ levels. Lower PPARγ levels were found in patients with BD than patients with schizophrenia and healthy controls (García-Álvarez et al. 2018). Contrary to this study, serum PPARγ levels were found to be significantly lower in patients with schizophrenia in the acute exacerbation episode than in healthy controls (Yüksel et al. 2019). While evaluating the serum markers in the BD, PPARγ values in the mania group was found to be significantly lower than both those of the remission and the control groups. There was no significant difference between PPARγ levels in the remission and control groups. This indicates that PPARγ is a state marker rather than trait marker in BD (Erzin et al. 2019). It was reported that in the pediatric population with BD the PPARγ levels were significantly lower than in the control group (Kasak et al. 2022). To date, only one family genetic study found that PPARδ, the gene that codes for the PPARδ receptor, is associated with BD (Zandi et al. 2008).

Diabetes, obesity, dyslipidemia, and Metabolic Syndrome (MetS) are very common in BD (Babić et al. 2010). Despite the prevailing view that psychotropic drug use causes MetS, the prevalence of diabetes, obesity, and MetS is elevated in BD, regardless of psychotropic drug use (McElroy & Keck 2012). It has been hypothesized that metabolic and mood disorders are two manifestations of the same multisystemic inflammatory disease (Li et al. 2019). Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1 α) alpha and PPARs are innovative potential targets both BD and MetS (Nierenberg et al. 2018). PPARγ agonist pioglitazone was associated with improvement in depressive symptoms and reduced cardio-metabolic risk. Reduction in inflammation may represent a novel mechanism by which pioglitazone modulates mood (Kemp et al. 2014).

It can be said that PPARγ has a main function on both metabolic parameters and neuropsychiatric disorders. The importance of PPARγ in psychiatric disorders is mostly interpreted through agonist treatments. In some studies, speculative results have been obtained regarding the location of this marker. The aim of the study is to reveal the possible differences in serum PPARγ levels between BD manic, depressive and euthymic patient groups and healthy controls. In addition, the relationship between PPARγ and metabolic parameters was explored.

SUBJECTS AND METHODS

Methods

A total of 121 male patients, who were diagnosed with BD-I according to Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria (44 in manic, 35 in depressive and 42 in euthymic states) and treated inpatient and/or outpatient clinics of Bakirkoy Mazhar Osman Mental Health and Neurological Diseases Education and Research Hospital were assigned in this study.

Severity of mania was evaluated with the Young Mania Rating Scale (YMRS). Bipolar depression was assessed with the 17-item Hamilton Depression Rating Scale (HAM-D); a severity score of 20 or greater was required for inclusion. Euthymic state was defined as YMRS ≤8 and HAM-D score ≤7 for at least 8 weeks. Metabolic syndrome criteria were applied which was published by The International Diabetes Federation (IDF) in 2006. These criteria are 1) Raised triglycerides ≥ 150 mg/dL, 2) Reduced HDL cholesterol < 40 mg/dL in males, 3) Raised blood pressure systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, 4) Raised fasting plasma glucose ≥ 100 mg/dL, 5) waist circumference Male ≥ 94 cm. Central obesity plus any two of the above factors are essential for the diagnosis (Alberti et al. 2006).

Clinical diagnoses were established by a consensus of two senior psychiatrists following a psychiatric interview according to DSM-5. The healthy control group was selected from the individuals who had to come to the outpatient clinic for obligatory psychiatric examination prior to employment and adoption applications. Forty-one healthy volunteers without a psychiatric condition or a first-degree relative with a psychiatric diagnosis, matched for age, gender, and smoking status were recruited in the study. All groups were included of male individuals between 18 and 65 years of age. Individuals with intellectual disability, dementia, any psychiatric disorder secondary to a medical condition, alcohol or substance use disorder, any medical condition affecting central nervous system (CNS); a personal history of atypical headaches, head trauma, chronic lung disease, renal disease, chronic hepatitis, thyroid disease, active cancer, cerebrovascular disease, epilepsy; acute infection or allergy, using medication including omega-3, aspirin or any other drug with anti-inflammatory activity were excluded from this study. Each participant of this study provided informed and written consent. Approval for the study was obtained from the Bakırkoy Dr. Sadi Konuk Training and Research Hospital" Ethics Committee with the protocol dated 11.09.2017 and 2017/264.

Following at least eight hours of fasting state, blood samples were drawn from each participant into 10 cm3 biochemistry tubes and the blood serum were separated in the laboratory. Blood samples were collected at the same time during morning that the assessment would be carried out. PPARγ, routine biochemical measures and hemogram tests were performed for each sample. Once sample results were completed, the accordingly.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS; SPSS Inc., Chicago, IL) version 26 for Windows. The categorical variables were stated as percentage and the continuous variables as mean ± standard deviation for normally distributed data and median (interquartile range) if data were not normally distributed. Chi-square test was used to compare categorical variables. Kolmogorov–Smirnov's test was used to assess whether the continuous data are consistent with the normal distribution. One-way analysis of variance (ANOVA) and post hoc Bonferroni's test were performed to compare continuous variables between groups for parametric values. For the non-parametric data, Kruskal–Wallis's test and Bonferroni's corrected Mann–Whitney's U tests were used for the comparison. Analysis of covariance (ANCOVA) was used in order to make an adjustment for the age and current mood state for the comparison between study groups. Pearson's and Spearman's correlation tests were used for the correlations between variables. The p measure under .05 is used to define the statistical significance.

Operation and calculation of PPARγ

Venous blood samples of patients were taken into tubes used for such purpose (13 100 5ml Vacutainer plastic SST gel tube, Code VT 367955 Becton Dickinson, Franklin Lakes, NJ) and were transported to the laboratory at +4 C. They were then inverted for five minutes at 4000 g and the separated serum samples were transferred to sterile Eppendorf tubes and stored at –80 C until the study day. Human PPARγ ELISA Kit was used. The PPARγ parameter was performed in the serum samples of the patients according to colorimetric measurement principle and the recommendations of the manufacturer. The method, in short, depends on the colorimetric measurement of the level of PPARγ via spectrophotometry in vitro quantitatively in human serums.

RESULTS

A total of 121 patients who were diagnosed as Bipolar Disorder-I according to DSM-5 diagnostic criteria, 44 in manic (BD-m), 35 in depressive (BD-d) and 42 (BD-e) in euthymic states were included in this study. Forty-one healthy volunteers (HC) who were similar for the age and smoking status with the BD group were included as the control group. Only the male subjects were included in the study. The mean age of the groups was similar (38.22 ± 11.37 years for BD-m, 41.54 ± 10.29 years for BD-d, 40.52 ± 10.90 years for BD-e and 39.02 ± 10.69 years for HC, p = .530). There was no statistically significant difference between the groups in terms of smoking ($\chi 2$ = 4.561, p = .207). Characteristics of groups are represented in Table 1.

Table 1: Clinical characteristics and levels of inflammatory markers in patients currently in a manic, depressive or euthymic state compared with healthy controls

	Manic (n=44)	**Depressive (n=35)**	**Euthymic (n=42)**	**Control (n=41)**	**p-value**
PPARγ (**µg**/ml) β	78.29±7.45	78.51±10.16	87.5±37.26	82.46±9.26	>0.05
Age (years)α	38.22±11.37	41.54±10.29	40.52±10.90	39.02±10.69	0.530 F=0.739
Duration of illness (years) β	9 (11)	16 (10)	12.5 (11)	-	0.009** x^2=9.471
YMRS score	37.38±7.21	-	0.09±0.3	-	<0.001**
HAM-D score	-	41.74± 4.55	0.26±0.66	-	<0.001**
Previous manic episodes	5.55±4.59	3.87±3.80	4.59±3.60	-	
Previous depressive episodes	1.68±1.39	4.88±3.66	2.06±1.65	-	
BMI (kg/m^2) α	27.59±6.58	27.56±4.06	27.28±5.14	26.03±3.47	0.459 F=0.868
Waist Circumference (cm)α	104.2±17,4	102.8±11.2	98.9±14.9	96.4±11.1	0.048* F=2.693
LDL (mg/dl)β	91.7±27.6	111.9±60.0	109.4±39.8	127.7±34.7	<0.001** x^2=20.767
Trigliserid (mg/dl) β	141.1±94.8	217.1±159.6	160.9±99.9	138.1±66.1	0.014* x^2=10.609
HbA1c (%)β	5.5±0.7	5.6±0.9	5.3±0.5	5.6±1.1	0.452 F=0.882
Smoking status (yes)¥	70.4%	68.5%	50.0%	63.4%	0.207
CRP (mg/L) β	0.53 (0.75)	0.24 (0.35)	0.15(0.16)	0.13 (0.15)	0.001** x^2=25.767
Leukocyte α	8.9±2.4	8.1±1.8	8.5±2.2	7.9±1.9	0.116 F=1.998
Albumin α	4.4±0.3	4.5±0.2	4.8±0.3	4.8±0.3	<0.001** F=19.023
Neutrophils level (10^3/uL) β	5.5±2.1	4.7±1.3	5.1±1.8	4.4±1.1	0.051 x^2=7.782
Lithium carbonate¥	2.2%(n=1)	62.9%	73.8%	-	
Valproic acid¥	4.5% (n=2)	28.6%	31%	-	
Carbamazepine¥	-	2.9%	2.4%	-	
Lamotrigine¥	-	17.1%	2.4%	-	
Antipsychotics¥	-	94%	76.2%	-	
Antidepressant¥	-	37.1%	-	-	

α One-way ANOVA, β Kruskal Wallis test and ¥Chi-squared test were used, *p<0.05, **p<0.01, BMI: Body Mass Index, YMRS: Young Mania Rating Scale, HAM-D: Hamilton Depression Rating Scale, RvD1: Resolvin D1, CRP: C-reactive protein, LDL: low density lipoprotein

* Duration of illness time is since first episode (mania, depression or hypomania)

Two of the patients in the manic state were treated with valproic acid (VA) and one with lithium (Li). The other 41 patients in the manic state did not receive any medical treatment. The patients in the euthymic and depressive states, however, were treated with antipsychotics, VA, Li, carbamazepine (CBZ) and lamotrigine. Treatment percentages of the patients in the depressive and euthymic states are shown in Table 1.

Mean serum levels of PPARγ are shown in Table 1 and comparisons are shown between groups in Table 2. There was no significant difference between all groups and in pairwise comparisons. PPARγ serum level is highest in the control group and then euthymic, manic and depressive episodes continue to decrease, respectively. Serum PPARγ levels in the manic, depressive and euthymic patients and control groups are shown in Figure 1.

Except for the parameters specified in the table, we could not obtain statistically significant results when PPARγ and all other parameters were compared with the control and when we compared the episode groups separately. Correlation between serum PPARγ levels and the clinical characteristics as well as the inflammatory markers are shown in Table 3.

When 121 patients were evaluated, the rate of having MetS was 41.3%. There was no significant difference ($\chi 2=5.09$, $p=0.165$) regarding having MetS between the

Figure 1: Serum PPARγ levels in the manic, depressive and euthymic patients and control groups.

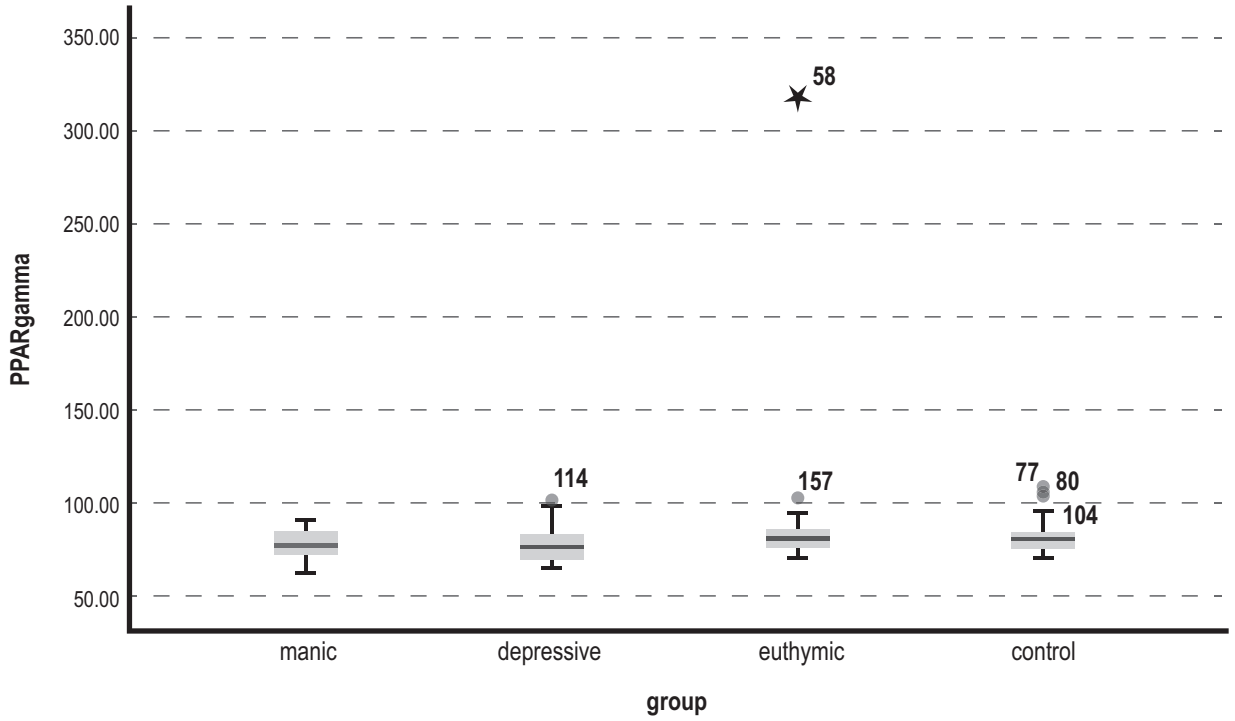

Table 2: Pairwise comparisons (p values) of serum PPARγ levels

	Test Statistic	Std. Error	Std. Test Statistic	p
Manic vs. Depressive	4.450	10.614	0.419	1.000
Manic vs. Euthymic	-20.548	10.109	-2.033	0.253
Manic vs. Control	-17.323	10.172	-1.703	0.531
Depressive vs. Euthymic	-24.998	10.725	-2.331	0.119
Depressive vs. Control	-21.773	10.784	-2.019	0.261
Euthymic vs. Control	3.224	10.288	0.313	1.000

Kruskal Wallis test was used. Signifiance values have been adjusted by the Bonferroni correction for multiple tests

Table 3: Correlation between serum PPARγ levels and the Clinical Characteristics as well as the Inflammatory Markers.

	r	p
LDL (mg/dl)	-0.784	0.022*
HbA1c (%)	-0,976	0.002**
Neutrophils level (10^3/uL)	0.986	0.001**
WBC (10^3 / uL)	-0.750	0.025*
TSH (mIU / L)	0.940	0.006**
fT3 (pg/ml)	0.763	0.024*
Creatinine (mg/dl)	0.944	0.006**
K (mmol/L)	0.944	0.006**
Age at first episode	-0.671	0.039*
Age at first treatment	-0,795	0.024*
Smoking	0.870	0.013*
Seasonality	-0.628	0.045*

Spearman correlation test was used *p<0,05, **p<0,01, r: Spearman correlation coefficient
LDL: low density lipoprotein, WBC: White blood cell, HbA1c: glycated haemoglobin,
TSH: thyroid stimulating hormone, fT3: Free Triiodothyronine, K: potassium

four groups. Moreover, there was no relationship between PPARγ and MetS parameters. Each group was divided into two subgroups to the presence of MetS. The relationship of MetS parameters, LDL, body mass index (BMI) and PPARγ levels between groups is shown in Table 4.

DISCUSSION

Although PPARγ has been studied previously in manic and euthymic episodes of BD, it is the first study in which depressive episode is included. There is no significant difference in serum PPARγ levels between BD-m, BD-d, BD-e and the heathy controls. According to presence of MetS, patients who have both depressive episode and MetS have significantly high level of PPARγ compared to depressive patients without MetS.

PPARs are believed to have a therapeutic effect by reducing inflammation, neurotransmitter modulation, and metabolic regulation in psychiatric disorders. Both schizophrenia and BD etiologies are significantly influenced by abnormalities in the immune system's dysregulation and the stress response system (Drexhage et al. 2011). Previous studies have shown that PPARγ is affected to varying degrees in schizophrenia and BD (Erzin et al. 2019, García-Álvarez et al. 2018, Yüksel et al. 2019). This indicates that the inflammatory route in the pathophysiology of BD may be more specifically regulated by PPARγ (García-Álvarez et al. 2018). In contrast, it is hard to say that PPARγ has a specific role in the BD according to this study's results. The positive relationship between PPARγ and neutrophils levels can be a sign that shows PPARγ tries to suppress inflammation. While evaluating the serum levels, it can be hypothesized that PPARγ is insufficient especially in manic and depressive episode. On the other hand, it is reported that pioglitazone injection to rats causes a decrease in WBC. According to the present study, the negative relationship between PPARγ and WBC supports this information.

Kasak et al. reported that the serum PPARγ level is significantly higher in BD than the healthy control group in pediatric population (PBD). They emphasized that this differences in the PPARγ levels could be related to MetS. Lower PPARγ activity and a higher frequency of MetS in PBD suggest dysregulation of immune and metabolic regulatory factors (Kasak et al. 2022). Also, Erzin et al. (2019) speculated that their results might be affected by the relationship of abdominal obesity measured by waist circumference and low-grade inflammation. In the present study, no significant difference in PPARγ among the four groups can be explained by the absence of MetS.

Table 4: The Distribution of the Metabolic Syndrome and Differences between the PPARγ levels and Metabolic Parameters in Each 4 groups

	Control			Mania			Depression			Euthymic		
	MetS(+) n=13	MetS(-) n=28	p	MetS(+) n=14	MetS(-) n=30	p	MetS(+) n=20	MetS(-) n=15	p	MetS(+) n=16	MetS(-) n=26	p
PPARγ mean level (µg/mL)	82.3±2.6	82.5±1.7	0.877β Z=-0.155	80.9±1.8	77.0±1.3	0.110α t=1.631 F=0.327	81.5±2.5	74.5±1.8	0.032* α t= 2.240 F=4.366	96.1±14.9	82.1±1.4	0.969β Z=-0.039
BMI (kg/m^2)	28.5±0.9	24.8±0.5	0.001**α t= 3.581 F=0.072	29.8±1.2	26.5±1.3	0.032*β Z=-2.142	28.9±0.7	25.6±1.0	0.014* α t= 2.596 F= 0.748	30.3±1.4	25.4±0.7	0.002**α t= 3.333 F= 3.065
Waist circumference (cm)	105.0±3.2	92.3±1.5	<0.001**α t= 3.970 F= 2.021	109.7±3.3	101.7±3.4	0.155α t=1.447 F=3.022	105.8±1.9	99.0±3.3	0.075 α t= 1.838 F= 3.150	109.2±3.2	92.5±2.4	<0.001**α t= 4.140 F= 0.078
SBP (mmHg)	126.1±2.8	116.1±1.7	0.006 **β Z=-2.743	122.2±2.7	116.1±1.3	0.061β Z=-1.874	119.5±1.6	113.3±2.3	0.026*β Z=-2.232	125.6±3.6	117.6±2.3	0.121β Z=-1.550
DBP (mmHg)	78.4±2.1	74.3±1.2	0.116β Z=-1.573	74.2±1.3	73.0±1.3	0.596β Z=-0.530	76.5±1.5	74.6±1.3	0.307β Z=-1.021	80.6±1.9	75.0±1.5	0.036*β Z=-2.095
FBG (mg/dL)	100.4±10.7	89.7±2.1	0.510β Z=-0.659	110.0±10.7	90.7±1.8	0.018*β Z=-2.358	97.8±3.6	91.9±5.3	0.102β Z=-1.635	102.7±8.7	97.3±3.8	0.143β Z=-1.466
LDL (mg/dL)	135.0±12.3	124.3±5.5	0.585 β Z=-0.547	97.7±7.6	88.9±4.9	0.331α t= 0.984 F=0.055	122.4±16.4	97.9±8.2	0.414β Z=-0.817	118.1±13.0	104.1±5.8	0.342 α t=0.973 F=4.697
HDL (mg/dL)	37.0±2.0	47.2±2.0	0.001**α t= -3.037 F= 4.342	33.5±1.5	47.9±2.1	<0,001**α t= -4.243 F= 3.057	32.3±1.5	46.2±2.6	<0,001**α t= -4.686 F= 2.141	37.9±2.5	49.0±2.3	0.004**α t=-3.048 F=0.305
TG (mg/dL)	198.1±18.1 (Max:320, min:89)	110.2±8.5	<0,001**β Z=-4.007	337.1±131.8 (Max:2016-min:102)	110.0±13.8	<0,001**β Z=-3.894	287.9±39.1 (Max:885, min:140)	122.8±15.3	<0.001**β Z=-4.051	250.5±23.6 (Max:392, min:86)	105.8±10.2	<0,001**α t= 5.616 F=11.476

Values are presented as number only or mean ± standard deviation

PPARγ: peroxisome proliferator-activated receptor gamma; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein cholesterol; TG: triglyceride; BMI: Body mass index

α :t test. β :Mann-Whitney U test, *p<0,05, **p<0,01

However, in BD-d, the PPARγ level is significantly higher in the group with Mets than the group without MetS. While observing the rates of the MetS in that four groups in the present study, the highest rate is seen in the depressive episode. It may be clear why PPARγ is high significantly in this group.

There is a significant association between medical burden and the severity of mood symptoms in BD. The number of affected organ systems and the degree of the depression at baseline were strongly correlated, and throughout a period of up to 24 weeks, a larger medical burden was linked to a slower improvement in measures of the intensity of the depressive symptoms (Kemp et al. 2010). Pioglitazone has been demonstrated to be beneficial in treating bipolar depression individuals with and without MetS for depressive symptoms (Kemp et al. 2014). Based on dysregulated inflammation and abnormal brain energy metabolism, it is suggested an indirect association between PPARγ and BD (Nierenberg et al. 2018). In the present study, a significant and negative correlation was found between PPARγ levels and HbA1c. According to this study, it can be suggested that PPARγ agonists may also be effective especially in depressive episode.

As the severity of the disease worsened in adult individuals with schizophrenia, it was shown that the PPARγ level decreased. Due to the chronic and destructive character of BD and schizophrenia, there may be an inverse association between disease duration, age, and PPARγ level (Yüksel et al. 2019). In the later stages of BD, the combination of long-term neuroprogression and increased systemic toxicity and inflammation may lead to deficiencies in compensatory mechanisms such as neurotransmitters and anti-inflammatory chemicals (Kapczinski et al. 2017). Higher long-term depressed morbidity, but not a worsening course, is predicted by an earlier age of onset. An individual's level of manic or depressive symptom persistence over a five-year period seems to be a stable trait, however this stability declines over time (Coryell et al. 2009). Early onset of BD is linked to characteristics that can have a detrimental impact on long-term results, such as higher comorbidity. However, no correlation between early onset and signs of treatment resistance or severity, such as psychotic symptoms, was observed. Clinical characteristics that might respond to pharmacological and psychological treatment were discovered to have the strongest correlation with early age of onset. The findings emphasize the need of early detection and offer possible areas for early intervention in BD to concentrate on (Joslyn et al. 2016). In the present study, negative significant differences between age at first episode, age at first treatment and PPARγ may demonstrate the importance of the early treatment in BD.

As a predictor of early relapse and a chronic course and prolonged duration of BD, a higher BMI has noticed. During the depressed episode of BD, metabolic abnormalities in general, and body weight in particular, may have a negative impact on treatment response (Joslyn et al. 2016). While evaluating the serum PPARγ levels we can mention that the group with Mets have higher levels than the group without Mets in the BD. It may be hypothesized as a reactive increase. Oral treatment of glycyrrhizic acid for 24 hours increased insulin sensitivity and lipid profiles which contains decreased LDL, as well as triggered elevation of total PPARγ and lipoprotein lipase expression levels in all tissues tested (Yoke Yin et al. 2010). In the present study, the negative relationship between PPARγ and LDL may be support for this research.

The nuclear hormone receptor superfamily's members share a lot of structural similarities, which has allowed for the discovery of a variety of in vitro interactions, particularly amongst nuclear receptors that control metabolism. PPAR and the thyroid hormone receptor (TR) are structurally related in several ways. The control of lipid metabolism may be significantly influenced by the interplay between TR and PPAR. T3 affects the expression of genes involved in a variety of metabolic pathways in the liver, including cell proliferation, gluconeogenesis, glucose utilization, glucose transport, and insulin signalling (Liu et al. 2007). The positive relationship between PPARγ and TSH with fT_3 are important finding for showing the direct effect among these parameters.

It was shown that PPARγ interacts with Nuclear Factor kappa B (NF-κB) under TNF-α exposure conditions, but this interaction was disrupted by smoking exposure, suggesting that smoking suppresses this crucial anti-inflammatory process involving PPARγ. The production of pro-inflammatory mediators caused by smoking is inhibited differently depending on whether PPARγ is activated with natural or synthetic ligands (Caito et al. 2008). Healthy smokers' monocytes and monocyte-derived macrophages exhibit constitutively increased PPARγ expression; nicotine can somewhat mimic this effect in vitro (Amoruso et al. 2007). Common PPARγ genotypes of variants was detected between smoking and increased cardiovascular risk (Ding et al. 2016). In the present study, the positive relationship between smoking and PPARγ may show the reactive excessive answer to this inflammatory process.

Our study has some limitations. First of all, the absence of longitudinal data to help investigating the behavior of serum PPARγ over time along with the clinical course is an important limitation. Therefore, long-term follow-up studies are needed. The reason why this study

included only male individuals is to avoid cyclical changes in hormones thus the inflammatory markers. It is previously reported that estrogen and progesterone suppress the microglial TNF-a secretion (Drew & Chavis 2000). A study investigating a possible relationship between affective symptoms and menstrual cycles recruited among female patients with BD reported that there was a significant correlation between the menstrual changes and affective symptoms in 65% of females (Rasgon et al. 2003). However, a population solely of males is not a true representative of the general population. In our study evaluating only PPARγ as a marker limits us in interpreting the data that we find. The low number of participants is also a limitation of our study.

CONCLUSIONS

We suggest that PPARγ may be a key factor in the BD depressive group with MetS. Not finding any relationship between the PPARγ levels and the episode of BD may be related with the absence of MetS in the individuals. The use of PPARγ agonists, especially in the treatment of bipolar depression, may be beneficial when evaluated together with the results of this study. In order to understand the role of PPARγ and its receptors in BD and MetS, there is a need for further studies with a structured design and a patient population representative of general BD population. MetS parametres must also be considered if PPARγ is to be evaluated in the future investigations.

Ethical Considerations

Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest

No conflict of interest

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