



## Research article

## The association between leptin and adiponectin, and metabolic syndrome components and serum levels of lipid peroxidation in bipolar disorder patients treated with lithium and valproic acid

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## ARTICLE INFO

## Keywords:

Public health  
Clinical genetics  
Internal medicine  
Laboratory medicine  
Clinical research  
Leptin  
Adiponectin  
Metabolic syndrome components  
Lipid peroxidation  
Bipolar disorder patients  
Lithium and valproic acid

## ABSTRACT

**Background:** The aim of study is to assess a relation between the adiponectin and leptin levels, and metabolic syndrome components and lipid peroxidation treated with Li and VPA in bipolar disorder patients and compared with controls.**Materials and methods:** 56 patients and 31 healthy controls were enrolled. The ATP III criteria were used to determine metabolic syndrome components. Leptin, adiponectin, lipid peroxidation and lipid profiles were measured.**Results:** Malondialdehyde in Li patients was higher than VPA patients. BMI, waist circumference (WC), triglyceride, malondialdehyde and adiponectin levels were increased, whereas HDL-cholesterol (VPA treated patients) and leptin were decreased in patients compared with controls. Leptin and adiponectin were correlated with WC, triglyceride and malondialdehyde in both groups. Adiponectin was correlated with HDL-cholesterol in VPA patients.**Conclusion:** Patients should be checked metabolic syndrome components, serum leptin and adiponectin level occasionally to prevent possible deficiency or pathologic increase of these parameters.

## 1. Introduction

The prevalence of metabolic syndrome (MetS) is high in bipolar disorder (BD) patients in the most of the countries which its prevalence changes from 16.7% to 67% [1, 2, 3]. Bipolar disorder is a disease characterized with severe symptoms of mood and thought Disorder [4]. Common risk factors have shown among BD and MetS patients. These risk factors are endocrine disturbances, sympathetic nervous system dysregulation, physical inactivity and overeating [5, 6]. Bipolar disorder patients show also at risk of obesity, metabolic syndrome, diabetes mellitus, dyslipidemia, hypertension and cardiovascular disease [7]. Oxidative stress shows with an imbalance between antioxidant and the

production of free radicals and reactive oxygen species (ROS). These compounds may damage cell components [8]. Under normal conditions, different kinds of antioxidants eliminate ROS. The oxidative cell injury may take place in proteins and DNA because of the failure of ROS elimination [9]. ROS may play an important role in damage of nerve cell components and may take part in the pathogenesis of BD. Studies have revealed that lipid peroxidation and antioxidants alternate in patients with BD [10]. Study of oxidative stress in BD is not exactly clear. Adipokines, such as leptin and adiponectin, are important mediators of energy homeostasis. Leptin and adiponectin have different functions such as glucose and insulin regulation, lipoproteins homeostasis and inflammatory activity [11, 12, 13]. Studies have been shown that abnormal

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levels of adipokines have been revealed in BD clinical study [14, 15, 16, 17, 18]. Leptin and adiponectin are known to influence many biological functions [13]. Leptin is a hormone synthesized and secreted from white and brown adipose tissue cells [19]. Leptin can regulate the balance between energy uptake and consumption. It has been indicated that leptin has many functions such as reproduction, haematopoiesis, and the regulation of gastrointestinal system functions, angiogenesis and the sympathetic nervous system [20]. It has been reported that leptin reduces intracellular lipid concentration by reducing the synthesis of fatty acids and triglyceride and increasing fat oxidation [14]. Leptin levels are elevated in obese subjects probably due to its resistance to action in the central nervous system [21]. Rats exposed to chronic unpredictable stress or chronic social defeat stress showed decreased basal levels of leptin in plasma [22]. Adiponectin is produced by adipocytes and enhances sensitivity of insulin and fat oxidation [23, 24]. Studies have shown that there are an association between adiponectin deficiency and the metabolic syndrome [25]. In obese subjects, adiponectin expression was decreased, and studies on animals had shown that obesity-related metabolic and cardiovascular disorders was protected by adiponectin [25]. A study indicated that increased level of adiponectin was considered among overweight BD patients when compared to overweight controls [26]. Some other studies have revealed that adiponectin may contribute to obesity, diabetes mellitus, dyslipidaemia, MetS, insulin resistance diseases [27]. The drugs used for treatment of BD such as mood stabilizers and antipsychotics may lead to weight gain and changes in lipid and glucose metabolism [28, 29]. Some studies have shown that MetS and BD are associated with a high risk of cardiovascular disease [6, 30, 31] and a two-fold increase in mortality [32]. Some pharmacological agents used in the treatment of BD such as lithium (Li) and valproic acid (VPA), carbamazepine and lamotrigine [33]. Studies have shown that therapeutic agents used in BD patients treatment such as Li and VPA. The common side effects of VPA treatment are weight gain, gastrointestinal symptoms, sedation, tremor and mild elevation of hepatic enzymes [34] which is associated with metabolic and endocrine abnormalities. Lithium uses for treatment of BD [35, 36, 37, 38]. Some studies have indicated a common side effect of Li is weight gain, which is shown in 25–62% of patients using this agent [39, 40, 41, 42, 43, 44, 45], but the exact side effect of Li on weight gain remains unclear. In this study, we measured the fasting levels of lipid peroxidation, adiponectin and leptin, triglyceride, total cholesterol, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C), blood sugar, blood pressure and waist circumference in the BD patients after a 90-day treatment period in 2 groups that each group receives Li and VPA, respectively. Bipolar disorder patients treated with lithium and valproic acid may be involved in the pathogenesis of the metabolic syndrome. The effects of these drugs on the metabolic syndrome components are exactly unclear. The alterations of metabolic syndrome components may differ in different ethnic groups. Thus, we aimed this study to assess if there were a relation between the adiponectin and leptin levels, and metabolic syndrome components and lipid peroxidation in patients with bipolar disorder disease treated with lithium and valproic acid and compare with healthy subjects.

## 2. Materials and methods

In this study, Fifty six patients with BD were chosen from among patients (From 200 patients) who were referred to 5<sup>th</sup> Education Hospital Neuropsychiatry department in Gorgan, Iran. Our study condition was different with other studies. The BD patients were new case and they used Li and VPA for 3 months. They used these drugs from the beginning of our study. The patients were chosen with causal method and if each patient had our study condition then we selected them for our study.

The study was done in the Metabolic Disorders Research Center, Department of Biochemistry and Biophysics, Gorgan Faculty of Medicine, Golestan University of Medical Sciences. The study was approved by Golestan University of Medical Sciences ethics committee (Ethic number:

IR.GOUMS.REC.1397.261). All subjects were in filled the written informed consent. It was obtained after an explanation of the aim of the study. The BD patients received 975 mg/day VPA (31 patients) or 600 mg/day Li (25 patients) monotherapy for three months. The length of illness of the patients was 3 months. Thirty one healthy subjects were included in this study. The healthy subjects were selected from among health care workers or from patients' relatives. There were no metabolic syndrome, no drug consumption and no some other diseases, etc among healthy subjects. All BD patients were diagnosed by psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [46]. Patient's medical records collected with the help of patient relative's information and general practitioners records. The NCEP ATP III criteria were used to determine metabolic syndrome components [47]. The exclusion criteria for BD patients were if they have severe physical illness, alcohol and substance dependence, the presence of immunodeficiency and immunologic abnormalities, neurological, kidney and liver diseases, hypertension, malignancies and any additional psychiatric disorder or mental retardation, psychotropic medications other than Li or VPA. Adiponectin, leptin and lipid peroxidation (expressed as malondialdehyde (MDA, MDA unit was expressed as nmol/ml)) levels were measured in BD patients and healthy subjects. Blood samples were obtained from all subjects after a 12 h fasting and centrifuged at 2000 r.p.m. Serum was stored at  $-80^{\circ}\text{C}$  until we use it for the analyses. Micro enzyme-linked immunosorbent assay (ELISA) was used for determination of adiponectin and leptin levels. A commercial Human ELISA kit (ZellBio GmbH, Germany) was used to measure serum adiponectin ( $\mu\text{g}/\text{mL}$ ). An LDN Diagnostics kit (Germany) was used to determine serum leptin ( $\text{ng}/\text{mL}$ ), according to the manufacturer's instructions. MDA levels were determined according to the Satoh method [48] and the spectrophotometric technique (JENWAY6305). Body mass index (BMI) measurement was done using the metric measuring scale and formula  $\text{weight (kg)}/\text{height (meters)}^2$ . Waist circumference was measured using a tape in centimeters. Blood pressure was measured with a digital blood pressure monitor in patients and in controls (Omron 70JCP; Omron Matsusaka, Mie-Ken, Japan). All study subjects to be needed 12 h fasting periods. According to ATP III criteria [47] diagnosis of metabolic syndrome, if the subjects have 3 or more of under mentioned criteria:

- Waist circumference higher than 102 cm in men and 88 cm in women.
- Fasting triglyceride level over 150 mg/dl.
- HDL cholesterol level less than 40 mg/dl in men and 50 mg/dl in women.
- Blood pressure higher than 130/85 mmHg.
- Fasting blood glucose (sugar) over 110 mg/dl.

Fasting blood sugar, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were determined by using a commercial kit made in Iran. All measurements were done using a spectrophotometric technique (JENWAY6305).

### 2.1. Statistical analysis

The SPSS Statistical Package was used to analyze the data (Version 16.0, Chicago, USA for Windows). The variables were assessed using chi-square test, independent samples t-test and Mann-Whitney U-test. Correlations between variables were done with the Pearson's correlation coefficient. The data were shown as mean  $\pm$  SD and percentage. The *p*-value lower than 0.05 was considered as statistically significant.

## 3. Results

Table 1 shows demographic and clinical characteristics of BD patients treated with Li and VPA. The mean age was  $40.0 \pm 13.38$  years and  $45.32 \pm 12.89$  years in patients received Li and VPA, respectively. During the three months treatment period with Li and VPA monotherapy in BD patients, there were no significant differences between genders, BMI,

**Table 1.** Demographic and clinical characteristics of bipolar disorder patients.

Parameters	Bipolar Disorder patients received lithium (n = 25)	Bipolar Disorder patients received valproic acid (n = 31)	P-value
Mean age (years)	40.0 ± 13.38	45.32 ± 12.89	0.260
<b>Gender</b>			
Male n (%)	18 (72)	18 (58.1)	0.203
Female n (%)	7 (28)	13 (41.9)	0.120
Body Mass Index (BMI)	27.58 ± 7.10	28.33 ± 5.04	0.480
waist circumference (cm)	95.92 ± 15.97	98.45 ± 12.16	0.504
Systolic blood pressure (mmHg)	113.72 ± 13.03	114.22 ± 14.05	0.891
Diastolic blood pressure (mm Hg)	75.00 ± 11.03	74.32 ± 8.70	0.740
Fasting blood glucose (FBS) (mg/dL)	92.96 ± 24.05	97.25 ± 21.66	0.44
Fasting serum triglyceride (mg/dL)	140.44 ± 56.36	160.70 ± 122.69	0.856
Total cholesterol (mg/dL)	171.32 ± 44.22	171.77 ± 39.59	0.746
Fasting lowdensity lipoprotein (LDL) cholesterol (mg/dL)	102.68 ± 31.56	102.48 ± 27.99	0.624
Fasting high density lipoprotein (HDL) cholesterol (mg/dL)	44.0 ± 8.74	41.77 ± 8.34	0.336
Leptin (ng/mL)	19.23 ± 20.73	24.15 ± 20.63	0.262
Adiponectin (µg/mL)	2.735 ± 0.937	2.99 ± 1.11	0.365
Malondialdehyde (MDA) (nmol/mL)	0.48 ± 0.02	0.43 ± 0.031	<0.01

The bold values are represents the  $P < 0.01$ .

metabolic syndrome components, leptin and adiponectin in two groups. Serum leptin and adiponectin levels were higher in bipolar disorder patients received VPA compared with those patients received Li ( $P > 0.05$ ). Serum malondialdehyde in BD patients received Li was significantly higher than those received VPA ( $P < 0.001$ ).

Table 2 shows demographic and clinical characteristics of BD patients received Li and healthy controls. The mean age in healthy controls was  $42.22 \pm 10.10$  years. BMI, waist circumference, fasting serum triglyceride, malondialdehyde and adiponectin levels were significantly higher in BD patients than healthy controls ( $P < 0.05$ ). The serum leptin was significantly higher in healthy controls than in BD patients. The other parameters showed no significant differences between two groups.

Table 3 shows demographic and clinical characteristics of BD patients received VPA and healthy controls. A significant increase was found in BMI, waist circumference, fasting serum triglyceride, adiponectin and malondialdehyde in BD patients compared with healthy controls ( $P < 0.05$ ), whereas HDL-cholesterol and leptin were significantly decreased in BD patients compared with healthy controls ( $P < 0.05$ ). The other parameters showed no significant differences between two groups.

Tables 4 and 5 show the correlation analyses between leptin and adiponectin levels and metabolic syndrome components and malondialdehyde in BD patients received Li and VPA, respectively. Leptin and adiponectin were significantly correlated with waist circumference, fasting serum triglyceride and malondialdehyde in both groups ( $P < 0.05$ ), whereas other parameters were not significantly correlated with any parameters (Table 4). Adiponectin was also significantly correlated with HDL-cholesterol in patients treated with VPA (Table 5,  $P < 0.05$ ). The prevalence of metabolic syndrome among bipolar disorder patients with Li and VPA monotherapy were 16% and 25.8%, respectively (not shown).

#### 4. Discussion

Lithium is used to decrease the recurrence of manic, depressive episodes [49]. Lithium also has been used in the treatment of BD patients for a long time. Its mechanism of effect is not exactly clear [50]. Valproic acid is used to prevent mania recurrence in BD. Its preventive effect has not been exactly defined [51]. Like Li, VPA may be used as a therapeutic drug for BD patients [52]. According to our study, the only

**Table 2.** Demographic and clinical characteristics of bipolar disorder patients received lithium and healthy controls.

Parameters	Bipolar Disorder patients received lithium (n = 25)	Healthy controls (n = 31)	P-value
Mean age (years)	40.0 ± 13.38	42.22 ± 10.10	0.312
<b>Gender</b>			
Male n (%)	18 (72)	16 (51.6)	0.311
Female n (%)	7 (28)	15 (48.4)	0.134
Body Mass Index (BMI)	27.58 ± 7.10	24.78 ± 4.43	<b>0.01</b>
waist circumference (cm)	84.0 ± 10.98	95.92 ± 15.97	0.003
Systolic blood pressure (mmHg)	117.19 ± 11.97	113.72 ± 13.03	0.304
Diastolic blood pressure (mm Hg)	78.54 ± 7.36	75.00 ± 11.03	0.180
Fasting blood glucose (FBS) (mg/dL)	90.29 ± 5.25	92.96 ± 24.05	0.418
Fasting serum triglyceride (mg/dL)	83.41 ± 33.08	140.44 ± 56.36	<b>&lt;0.001</b>
Total cholesterol (mg/dL)	167.77 ± 29.61	171.32 ± 44.22	0.348
Fasting low density lipoprotein (LDL) cholesterol (mg/dL)	99.21 ± 22.19	102.68 ± 31.56	0.275
Fasting high density lipoprotein (HDL) cholesterol (mg/dL)	47.29 ± 7.66	44.0 ± 8.74	0.146
Leptin (ng/mL)	54.20 ± 14.48	19.23 ± 20.73	<b>0.001</b>
Adiponectin (µg/mL)	2.48 ± 0.61	2.735 ± 0.937	<b>0.01</b>
Malondialdehyde (MDA) (nmol/mL)	0.40 ± 0.06	0.48 ± 0.02	<b>0.013</b>

The bold values are represents the  $P < 0.001$ ,  $P < 0.001$ ,  $P < 0.01$ ,  $P < 0.013$ , respectively.

**Table 3.** Demographic and clinical characteristics of bipolar disorder patients received valproic acid and healthy controls.

Parameters	Bipolar Disorder patients received valproic acid (n = 31)	Healthy controls (n = 31)	P-value
Mean age (years)	45.32 ± 12.89	42.22 ± 10.10	0.258
<b>Gender</b>			
Male n (%)	18 (58.1)	16 (51.6)	0.213
Female n (%)	13 (41.9)	15 (48.4)	0.217
Body Mass Index (BMI)	28.33 ± 5.04	24.78 ± 4.43	<b>0.01</b>
waist circumference (cm)	98.45 ± 12.16	84.0 ± 10.98	<b>&lt;0.001</b>
Systolic blood pressure (mmHg)	114.22 ± 14.05	117.19 ± 11.97	0.374
Diastolic blood pressure (mm Hg)	74.32 ± 8.70	78.54 ± 7.36	0.398
Fasting blood glucose (FBS) (mg/dL)	97.25 ± 21.66	90.29 ± 5.25	0.762
Fasting serum triglyceride (mg/dL)	160.70 ± 122.69	83.41 ± 33.08	<b>&lt;0.001</b>
Total cholesterol (mg/dL)	171.77 ± 39.59	167.77 ± 29.61	0.476
Fasting lowdensity lipoprotein (LDL) cholesterol (mg/dL)	102.48 ± 27.99	99.21 ± 22.19	0.218
Fasting high density lipoprotein (HDL) cholesterol (mg/dL)	41.77 ± 8.34	47.29 ± 7.66	<b>0.009</b>
Leptin (ng/mL)	24.15 ± 20.63	54.20 ± 14.48	<b>0.001</b>
Adiponectin (µg/mL)	2.99 ± 1.11	2.48 ± 0.61	<b>0.001</b>
Malondialdehyde (MDA) (nmol/mL)	0.43 ± 0.031	0.40 ± 0.06	<b>0.030</b>

The bold values are represents the p<0.001, p<0.001, p<0.009, p<0.001, p<0.001, p<0.01, respectively.

**Table 4.** Correlations between leptin and adiponectin levels and metabolic syndrome components and malondialdehyde level in bipolar disorder patients received lithium.

Parameters	Leptin (ng/mL)		Adiponectin (mg/ml)	
	correlation coefficient (r)	p-value	correlation coefficient (r)	p-value
waist circumference (cm)	-0.288	<b>0.016</b>	0.259	<b>0.015</b>
Systolic blood pressure (mmHg)	-0.210	0.313	0.245	0.238
Diastolic blood pressure (mm Hg)	0.020	0.923	0.267	0.197
Fasting blood glucose (FBS) (mg/dL)	0.234	0.260	0.375	0.065
Fasting serum triglyceride (mg/dL)	-0.317	<b>0.020</b>	0.057	<b>0.006</b>
Fasting high density lipoprotein (HDL) cholesterol (mg/dL)	-0.071	0.738	0.217	0.298
Malondialdehyde (nmol/mL)	-0.394	<b>0.035</b>	-0.314	<b>0.027</b>

The bold values are represents the p<0.001, p<0.05.

**Table 5.** Correlations between leptin and adiponectin levels and metabolic syndrome components and malondialdehyde level in bipolar disorder patients received valproic acid.

Parameters	Leptin (ng/mL)		Adiponectin (mg/ml)	
	correlation coefficient (r)	p-value	correlation coefficient (r)	p-value
waist circumference (cm)	0.099	<b>0.042</b>	0.047	<b>0.018</b>
Systolic blood pressure (mmHg)	0.018	0.925	0.266	0.149
Diastolic blood pressure (mm Hg)	-0.069	0.713	-0.203	0.273
Fasting blood glucose (FBS) (mg/dL)	0.297	0.105	-0.277	0.132
Fasting serum triglyceride (mg/dL)	0.217	<b>0.024</b>	0.387	<b>0.003</b>
Fasting high density lipoprotein (HDL) cholesterol (mg/dL)	0.098	0.601	0.415	<b>0.020</b>
Malondialdehyde (nmol/mL)	0.424	<b>0.018</b>	0.274	<b>0.028</b>

The bold values are represents the p<0.01, p<0.001, p<0.05, p<0.05\*P<0.05, \*\*P<0.01, \*\*\*P<0.001.

malondialdehyde level was significantly higher in Li treated BD patients than those treated with VPA. It is maybe mean that Li has more effect on antioxidant defense system than VPA.

In our study, comparison of BD patients treated with Li and VPA with healthy controls showed that BMI, waist circumference, serum triglyceride, malondialdehyde and adiponectin were significantly higher and HDL-cholesterol (Only VPA treated patients) and leptin was significantly lower. Our study suggests that Li and VPA may effect on these parameters compared to healthy controls. These alterations may cause the elevated risk for metabolic complications. The clinical studies on metabolic syndrome in patients with BD has been limited. Studies of pylvanen [53] on associations between the metabolic effect of VPA therapy and insulin

levels alteration have shown that VPA therapy can cause weight gain and increases insulin level. A study has revealed that patients on medications for BD showed a significantly increased waist circumference, and serum triglyceride, and lower serum HDL-cholesterol than the controls [54] which is in accordance with our study. Study of Elmslie et al. in overweight patients with BD taking VPA and control subjects without psychiatric disorders showed that the frequency of metabolic syndrome was not statistically significantly higher in the patients with BD treated with VPA than in the control subjects [55]. Some studies have indicated that patients treated with Li had a higher prevalence of MetS than those treated with VPA [56]. According to our finding, the prevalence of metabolic syndrome was not high in VPA and Li treated patients

compared to other populations [1, 2, 3]. The prevalence of metabolic syndrome in VPA therapy patients was higher (25.8%) than in Li therapy patients (16%), which their findings were not in accordance with our study [1, 2, 3]. It may mean that the VPA may have more effect on metabolic syndrome component than Li which may cause more metabolic complications and may increase some metabolic risk factors. There may be other factors that they can affect the metabolic syndrome components in the patient with VPA and Li therapy. The nutritional habits, physical activity, sedentary life and genetic factors may be an effective factor. Our study showed that adiponectin in BD patient taking VPA and Li increased compared to healthy controls. High level of adiponectin in these patients may increase obesity factors such as waist circumference, triglyceride, decrease HDL-cholesterol (metabolic syndrome components) and BMI. These alterations may depend on the use of VPA and Li metabolic effect on obesity factors in BD patients that it may lead to change metabolic syndrome components, as it showed in Tables 2 and 3. Our findings are not in agreement with the results of some other studies. They showed that plasma adiponectin levels were higher in non-obese than the obese subjects [57]. Yang et al. was reported that Lower adiponectin levels were to be associated with higher serum triglycerides and low HDL-cholesterol [58] which is not in accordance with our findings. The association of Li and metabolic syndrome is not exactly understood. Some studies have shown the link between Li and metabolic dysregulation [59]. Some other studies have shown that Li induced decreases in adiponectin level was seen in BD patients after six weeks Li therapy [60]. In our study, there was a significant increase in adiponectin level in BD patients after 12 weeks Li and VPA therapy. The increase of serum adiponectin in Li and VPA treated patients may depend on longer time of Li and VPA monotherapy in our study. Lower adiponectin levels also have been reported in metabolic syndrome which was associated with Li treatment [41, 44, 45]. These studies were not in accordance with our study. Some studies have indicated that adiponectin may contribute to obesity, diabetes mellitus, dyslipidaemia and metabolic syndrome [27]. Study of pylvanen [53] showed that obese patients taking VPA and obese control subjects indicated higher serum level of leptin than underweight and poor subjects. Their study on obese patients taking VPA and obese control subjects, or between lean patients taking VPA and lean control subjects showed no change in leptin levels [53]. In our study, patient's treatment with VPA and Li and lower leptin levels in BD patients are associated with metabolic syndrome components (waist circumference and triglyceride) which is not in accordance with study of pylvanen [53]. Some studies have been demonstrated that leptin is involved in sleep regulation, sexual behavior and impulsivity. The findings caused many studies to show the role of leptin in psychiatric disorders such as depression and BD [61, 62]. A study has shown that patients with BD seems to be associated with decreased serum leptin levels [63]. The findings of some other studies indicated that serum level of leptin in patients with depression were not correlated with body mass index [64], while other studies have revealed that leptin plasma concentrations were not changed in depression and there was no association between the role of leptin and the loss of body weight in depressed patients [65]. In this study, serum leptin levels were significantly lower in BD patients taking VPA and Li compared to healthy controls and also there were correlated between leptin and waist circumference, triglyceride and malondialdehyde in patient treated with VPA (there was also a correlation between leptin and HDL-cholesterol) and Li. These alterations may be depend on the use and the effect of these drugs on the leptin level in BD patients that it may lead to change metabolic syndrome components. Our study shows that Li and VPA may the primary factor for low leptin levels in BD patients. Lower leptin levels and use of these drugs for a long time, may be caused leptin deficiency in BD patients. According to our study conditions, the correlation between leptin and TG is different in patients with VPA and Li therapy. The drug therapy may change leptin metabolism in BD patients. Thus, leptin showed negative and positive correlation with TG in Li and VPA treated patients after these drugs monotherapy for 3

months in our study. This correlation may also depend on new case study, different drug doses, and genetic differences. Some studies have revealed that the most obese patients have higher leptin levels [65], which is not in agreement with our findings. Some studies have been shown that oxidative stress seem to be an important factor in the pathogenesis of many psychiatric disorders [10, 66]. It is reported that oxidative stress took place in overweight patients after one year of VPA therapy. They indicated that obese patients with VPA therapy had higher serum MDA levels than non-obese patients treated with VPA and controls [67], which is in agreement with our finding. The increase in the level of MDA, may be happened with VPA or Li therapy effect or bipolar disorders. A study revealed that VPA therapy may increase the free radicals. This may initiate tissue injury, acute pancreatitis and hepatotoxicity [66]. In our study, MDA level was significantly higher in patients with VPA and Li therapy than in healthy controls. High serum MDA level in BD patients also suggests that VPA and Li treatment change lipid peroxidation. The elevated lipid peroxidation may increase the oxidation of lipid molecules. Biochemical studies showed that reactive oxygen species may change and interact with proteins and lipids [68]. According to our study conditions, the effect of MDA on adiponectin and leptin may different in patients with VPA and Li therapy. The drug therapy may change adiponectin and leptin metabolism in BD patients in this study condition. Thus, MDA has negative and positive correlation with adiponectin and leptin, respectively.

There were some limitations in our study. The first was the limited number of patients enrolled in this study. The second was the side effects of VPA and Li that they are not exactly cleared. Third was the effect of genetic factors that we did not determine its effect on BD patients in this study.

## 5. Conclusion

According to this study, patients taking VPA and Li monotherapy, leptin and adiponectin appeared to be associated with a significant change in metabolic syndrome components and malondialdehyde. However, the VPA treated patients were more affected than those Li treated patients. It seems that VPA and Li therapy for a long time may cause to increase malondialdehyde level and this may change leptin and adiponectin levels in BD patients.

It suggests that patients should be checked metabolic syndrome components, serum leptin and adiponectin level alterations occasionally to prevent any possible deficiency or pathologic increase of these parameters.

## Declarations

### Author contribution statement

A. Marjani: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

J. Yuzugulen: Conceived and designed the experiments.

M. Kamkar and T. Amirani: Analyzed and interpreted the data.

N. Dolab: Performed the experiments.

M. Marjani: Contributed reagents, materials, analysis tools or data; Wrote the paper.

### Funding statement

This work was supported by the Research Deputy of Golestan University of Medical Science.

### Competing interest statement

The authors declare no conflict of interest.

## Additional information

No additional information is available for this paper.

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