Lipid Peroxidation and Serum Antioxidant Enzymes Activity in Patients with Bipolar and Major Depressive Disorders

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ÖZET:

İki uçlu bozukluk ve major depresif bozuklukta lipid peroksidasyon ve serum antioksidan enzim aktiviteleri

Amaç: Mizaç bozuklukları araştırmalarında lipid peroksidasyonu ve antioksidanların durumu ilgi uyandırmaktadır. Bu alandaki sorulara yeni bir bakış açısı getirmek amacıyla, serum lipid peroksidasyon ürünleri (MDA) ve antioksidan enzimler süperoksit dismutaz (SOD) ve glutatyon peroksidaz (GPX), etkinliğindeki değişiklikler, iki uçlu bozukluk ve tek uçlu depresyon hastalarında ölçüldü. Bu çalışma mizaç bozukluğu olan hastalarda oksidatif stres ve antioksidan yanıtı değerlendirmek amacıyla yapılmıştır.
Yöntem: Çalışmada 71 mizaç bozukluğu (39 iki uçlu bozukluk ve 32 tek uçlu depresyon) hastasında plazma MDA ve antioksidan enzim aktiviteleri (SOD ve GPX) düzeyleri ölçülmüş ve sonuçlar sağlıklı kontrollerle (n=30) karşılaştırılmıştır. MDA tiyobarbitürik asitle reaksiyon veren substratlar üzerinden, GPX aktivitesi Paglia ve Valentine yöntemi ile, SOD aktivitesi Sun ve arkadaşlarının metoduna göre ölçüldü.
Bulgular: Serum SOD ve GPX aktiviteleri bakımından kontrol grubu ile karşılaştırıldığında iki uçlu ve tek uçlu depresif hastalarda belirgin biçimde azalmış olarak bulunurken, iki uçlu bozukluk ve tek uçlu depresif hastalar arasında fark bulunmadı ($p<0.05$). Buna karşın serum MDA konsantrasyonu sağlıklı grup ile karşılaştırıldığında iki uçlu ve depresif hastalarda artmış olarak saptandı ($p<0.05$). İki uçlu ve depresif hastalar arasında MDA düzeyleri bakımından farklılık saptanmadı.
Sonuç: Bu çalışmada iki antioksidan savunma enzim aktivitesinin düşük olarak bulunması mizaç bozukluklarında artmış oksidatif stresin varlığına işaret etmektedir. Sonuçlarımız oksidatif stres ile ilişkili reaktif oksijen ürünlerinin artmış üretimi lipid oksidasyonunu indükleyebileceği ve dolayısıyla antioksidan savunma sisteminin bu yolla zayıflamış olabileceğine işaret etmektedir.

Anahtar sözcükler: Mizaç bozuklukları, iki uçlu bozukluk, tek uçlu depresyon, oksidatif stres, lipid peroksidasyonu, duygudurum bozuklukları

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ABSTRACT:

Lipid peroxidation and serum antioxidant enzymes activity in patients with bipolar and major depressive disorders

AIM: Lipid peroxidation and antioxidant status are becoming attractive areas of research in mood disorders. To add a new insight to the question, changes in the serum lipid peroxidation products (MDA) and activities of antioxidant enzymes superoxide dismutase (SOD), glutathione peroxidase (GPX), were measured in patients with bipolar disorder and unipolar depression. This study was undertaken to assess oxidative stress and antioxidant status in patients with mood disorders.
Method: The study was conducted in 71 mood disorder patients (39 bipolar disorder and 32 unipolar depression) and compared to healthy controls (n=30). Levels of plasma MDA and activities of antioxidant enzymes SOD and GPX were measured. MDA was determined as the measure of thiobarbituric acid reactive substances. GPX activity was measured by the method of Paglia and Valentine. SOD activity was determined according to the method of Sun and colleagues. These parameters were measured in 71 patients and compared to controls.
Results: Serum SOD and GPX activities was strongly decreased in bipolar and depressed patients when compared to control group ($p<0.05$), but there was no difference between bipolar and depressed patients. Conversly, serum MDA concentration was siginificantly increased in bipolar and depressed patients when compared to control group ($p<0.05$), but there was no difference between bipolar and depressed patients.
Conclusions: Decreased activities of two antioxidant defense enzymes in the present study indicate an increased oxidative stress in mood disorder. Our results suggesting that the generation of reactive oxygen species associated with the oxidative stress may induce lipid oxidation and consequently decreasing antioxidant defence in mood disorders.

Key words: Mood disorders, bipolar disorder, unipolar depression, oxidative stress, lipid peroxidation

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INTRODUCTION

Experimental investigations have provided evidence supporting the role of reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide and hydroxyl radical in the etiology of mood disorders (1,2). Major sources of ROS in cell are electron leakage from transport chains in mitochondria and endoplasmic reticulum (3). Neurons are generally defenseless to free radical attack and impaired antioxidant system or exposure to excess

free radicals can initiate disruptive reactions with substrates that are important to the survival of cells such as proteins, lipids, nucleic acids and lead to neuronal death (4). More recently, oxidative stress has been implicated and there is evidence accumulating to support its' role in mood disorders (5-7).

Malondialdehyde (MDA), the end product of lipid peroxidation, arising from the free radical degradation of polyunsaturated fatty acids, can cause cross-linking in lipids, proteins and nucleic acids (8-10). Superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) form an antioxidant defense system against radical mediated damage and protect from cellular and molecular damage (10-12).

The present case control study was to examine the possible role of lipid peroxidation and the primary antioxidant enzymes in the pathogenesis of mood disorders.

MATERIALS AND METHODS

Patients

Thirty nine patients with euthymic bipolar disorder and thirty two patients with unipolar depression were consecutively recruited from the outpatients unit. Mood disorders were screened for respective diagnostic criteria as derived from Structured Clinical Interview the Patient Version of the DSM-IV (13). All patients and controls (n=30) gave informed consent for participation to the study. Characteristics of the study population included in the study are presented in Table 1.

MDA Measurement

Lipid peroxidation levels were determined by measuring the end product of lipid peroxidation MDA with thiobarbituric acid Schimadzu UV 1601 spectrophotometer (14). Serum MDA values were calculated using the extinction coefficient of MDA-thiobarbituric acid complex at 532 nm. MDA results were expressed as nmol/ml.

GSH-Px Measurement

GSH-Px activity was measured by the method of Paglia and Valentine (15). The enzymatic reaction was initiated by adding H_2O_2 to the reaction mixture containing reduced glutathione, reduced nicotinamide adenine dinucleotide phosphate and glutathione reductase. The change in the absorbance at 340 nm was monitored by Schimadzu UV 1601 spectrophotometer. One unit of GSH-Px is defined as micromoles of NADPH oxidized per minute. Activity was given in units per liter plasma volume.

SOD Measurement

SOD activity was determined according to the method of Sun and colleagues (16). One unit of SOD was defined as the amount of enzyme causing 50% inhibition in the NBT reduction rate. Activity was given in units per liter plasma volume.

Statistical Analysis

Data were analysed using SPSS 10.0 Version for windows statistical software (SPSS Inc. Chicago, Illinois, USA). Between-group comparisons were made by Student's t-test. Comparison of SOD, GSH-Px and MDA levels according to sex, lithium medication and duration were assessed with Mann–Whitney U-test. Data were presented as mean±SD. $p<0.05$ was considered statistically significant.

RESULTS

Serum SOD activity was significantly decreased in bipolar (3.6±1.1) and depressed (4.1±1.2) patients when

Table 1: Characteristics of the study population

	Bipolar (n=39)	Major Depression (n=32)	Control (n=30)
Sex (Male/Female)	20/19	11/21	15/15
Age (years)	38.3±13.4	35.5±13.7	36.1±12.2
Duration of illness (years)	9.0±10.0	-	-
Age of onset (years)	29.3±12.1	-	-
Hospitalization number	3.7±2.4	-	-

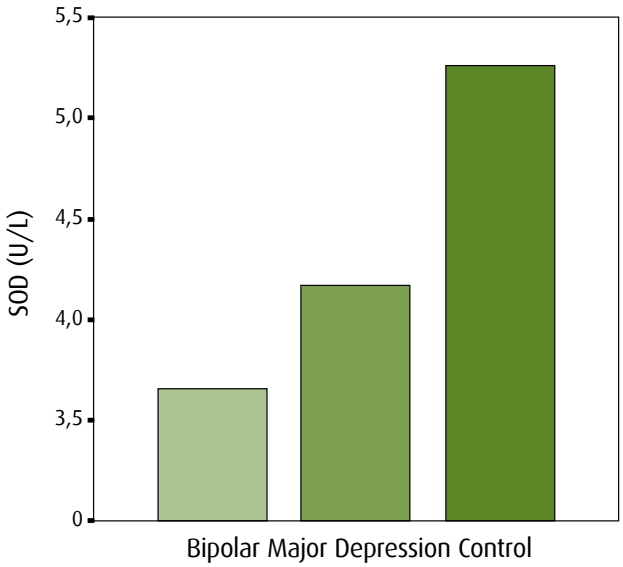

Figure 1: Serum SOD levels in study population

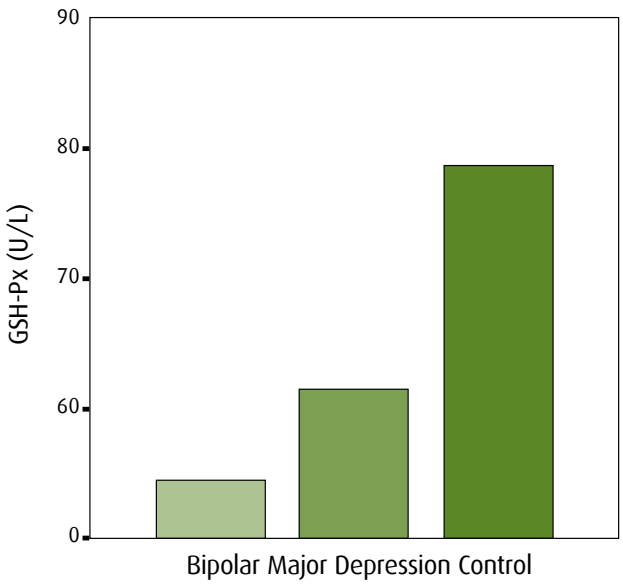

Figure 2: Serum GSH-Px levels in study population

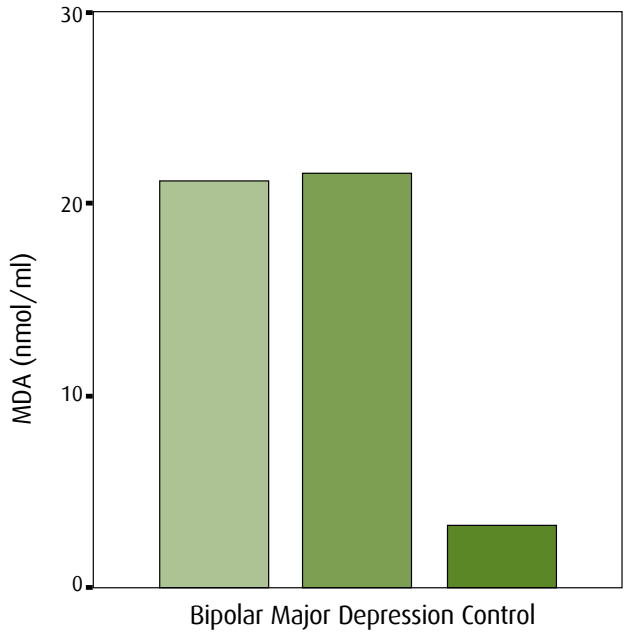

Figure 3: Serum MDA levels in study population

compared to control group (5.2±1.3, p<0.05), but there was no difference between bipolar and depressed patients (Fig 1). Similar to SOD activity, GSH-Px level was significantly decreased in bipolar (54.5±30.4) and depressed (61.6±33.0) patients when compared to control group (78.6±27.1, p<0.05), but there was no difference between bipolar and depressed patients (Fig 2). Conversly, serum MDA concentration was siginificantly increased in bipolar (21.1±10.7) and depressed (21.6±11.7) patients when compared to control group (3.2±1.6, p<0.05), but there was no difference between bipolar and depressed patients (Fig 3).

Serum SOD, GSH-Px and MDA levels were analysed in bipolar patients to determine the difference between male and female, duration of illness or lithium medication (Table 2), but no significant difference was found between

Table 2: Comparison of SOD, GSH-Px and MDA levels according to sex, lithium medication and duration of illness in Bipolar patients

	SOD	GSH-Px	MDA
Sex			
Male (n=20)	3.2±1.2	53.8±23.8	23.7±11.9
Female (n=19)	3.9±0.9	56.3±38.0	19.3±9.3
Duration of illness			
0-5 years (n=19)	3.6±1.3	57.8±35.0	21.1±11.7
>5 years (n=20)	3.6±1.0	52.5±37.1	21.9±10.0
Lithium medication			
Used (n=14)	3.7±1.1	62.0±37.8	21.9±12.9
Not used (n=25)	3.5±1.2	50.7±26.0	21.2±9.5

Table 3: Comparison of SOD, GSH-Px and MDA levels according to sex and medication in patients with major depression

	SOD	GSH-Px	MDA
Sex			
Male (n=11)	3.9±1.2	63.8±30.7	17.8±11.7
Female (n=21)	4.2±1.1	60.5±34.7	23.4±11.5
Medication			
AD (n=21)	4.0±1.3	62.7±37.6	24.3±11.1*
AD+AP (n=11)	4.1±1.0	67.7±29.3	12.7±5.9

AD antidepressant, AP antipsychotics ,*p<0.05

these groups (p>0.05).

Serum SOD, GSH-Px and MDA levels were analysed in bipolar patients to determine the difference between male and female or medication (Table 2). We did not find any significant difference between male and female subjects (p>0.05). No significant difference was detected in SOD and GSH-Px between medication groups (p>0.05). However, a significant difference was noted between medication groups in MDA concentrations (p<0.05).

DISCUSSION

In our study, we found decreased activities of SOD and GSH-Px in patients with major depression and bipolar disorder. Our findings are in accordance with other studies which showed a decreased levels of plasma SOD and GSH-Px in mood disorders (17,18). On the contrary, there are reports in the literature that found no difference in SOD or GSH-Px activity between mood disorder patients and healthy controls (19,20). Also, increased levels of plasma SOD and GSH-Px from patients with mood disorder have been reported (21,22). These results are contradictory, with lower, elevated or normal activities in mood disorders and discordance in these parameters may be due to several factors such as differences in the measurement of the methods, differences in medication and stage of the patients.

Decreased activity of two antioxidant defense enzymes in the present study indicate an increased oxidative stress in mood disorder. On the other hand, plasma MDA levels in patient groups were increased six to seven fold compared to normal controls provided further evidence that increased lipid peroxidation and thus oxidative stress existed. This finding of an elevation in plasma levels of MDA is consistent with the majority of studies of mood disorder with increased lipid peroxides (19,21). Lipid peroxidation in biological membranes causes loss of fluidity, decrease in membrane potential, increased permeability to ions and eventual rupture leading to release of cell and organelle contents (23). Consequently, this process could lead to neuronal membrane instability and perhaps cell death (2,24).

Lithium and valproate has been shown an antioxidant effect by mood stabilizers on cultured neural cells in excitotoxic conditions (25,26). On the other hand, lithium was not able to protect against the oxidative stress in the rabbit hippocampus (27). Thus, it is not clear which of these medications are associated with oxidative stress observed in the treated patient. Our data indicate that the potential oxidative damage in bipolar disorder patients was not prevented by mood stabilizers.

It has been reported that antidepressant treatment may suppress immune cells (28). Furthermore, antidepressants inhibit P450 enzymes which contribute to oxidative stress. It may be concluded that antidepressants may decrease antioxidant enzyme levels via reducing immune cells and inhibiting the P450 enzyme system. We found significantly decreased SOD and GSH-Px activity with paralel marked increase in MDA. However, patients using antipsychotics combination with antidepressants shows significantly decreased concentration of MDA and increased activity of SOD and GSH-Px but not statistically significant when compared with patients using antidepressants alone. Consequently, it may be speculated that alteration in antioxidant enzymes may cause this result and additionally antipsychotic combination or adjunct therapies may help to overcome the oxidative stres. This result opens a new gate for the discussions about the role of antipsychotics in Unipolar depression.

In conclusion our results suggesting that the generation of ROS associated with the oxidative stress may induce lipid oxidation, and consequently decreasing antioxidant defence in mood disorders.

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