Original article / *Araştırma*

Dynamic thiol/disulphide homeostasis as a novel oxidative stress marker in women with major depressive disorder

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ABSTRACT

Objective: *We aimed to investigate the oxidative stress status in a population of women with untreated major depressive disorder.* ***Methods:*** *Fifty-four female patients with untreated major depressive disorder and 68 female healthy controls were included in the study. A Sociodemographic Form, the Hamilton Anxiety Rating Scale, and the Hamilton Depression Rating Scale (HAM-D) were applied to all the participants. Fasting blood samples were collected from all participants to assess serum thiol/disulphide levels and their pairwise ratios.* ***Results:*** *Native thiol levels were significantly higher and disulphide levels were lower in patients as compared to controls, while total thiol levels were not significantly different between the groups. Disulphide/native thiol and disulphide/total thiol ratios were significantly lower, while the native thiol/total thiol ratio was significantly higher, in the patient group than the control group. There was a negative correlation between HAM-D score and disulphide level, disulphide/native thiol ratio, and disulphide/total ratio, while there was a positive correlation between HAM-D score and native/total thiol ratio, in the patient group.* ***Discussion:*** *This is the first study to investigate dynamic thiol/disulphide homeostasis in women with untreated major depressive disorder. Our results showed dynamic thiol/disulphide homeostasis shifts towards thiol formation which implies an antioxidant reaction in women with untreated major depressive disorder.* ***(Anatolian Journal of Psychiatry 2018; 19(2):135-142)***

Keywords: *depression, oxidative stress, female, thiol, disulphide*

Majör depresif bozukluk tanılı kadın hastalarda yeni bir oksidatif belirteç olarak tiyol/disülfid dengesi

ÖZET

Amaç: *Bu çalışmada majör depresif bozukluğu olan kadın hastalarda oksidatif stres durumunu değerlendirmeyi amaçladık.* ***Yöntem:*** *Çalışmaya ilaç tedavisi görmeyen majör depresif bozukluğu olan 44 kadın hasta ve 68 sağlıklı kadın alındı. Sosyodemografik Form, Hamilton Anksiyete Derecelendirme Ölçeği, Hamilton Depresyon Derecelendirme Ölçeği (HAM-D) tüm örneklemlere uygulandı. Serum tiyol/disülfid düzeyleri tüm katılımcılardan alınmış açlık kan örnekleri değerlendirilerek ölçüldü.* ***Bulgular:*** *Serum native tiyol düzeyleri hasta grubunda kontrol grubuna göre anlamlı düzeyde daha yüksek saptanırken, serum disülfid düzeyleri anlamlı düzeyde daha düşük saptandı. Serum total tiyol düzeyleri açısından gruplar arasında anlamlı fark yoktu. Hasta grubunda serum disülfid/native tiyol ve serum disülfid/total tiyol oranları anlamlı düzeyde düşük iken, serum native tiyol/total tiyol oranı anlamlı düzeyde yüksek saptandı. Hastaların HAM-D puanı ve serum disülfid düzeyi, disülfid/native tiyol oranı, disülfid/total tiyol*

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oranı arasında negatif korelasyon, HAM-D puanı ve serum native tiyol/total tiyol oranı arasında pozitif korelasyon vardı. ***Tartışma:*** *Çalışmamız tedavisiz majör depresyon tanılı kadınlarda dinamik tiyol/disülfid dengesini inceleyen ilk çalışmadır. Çalışmamızın sonuçları tedavisiz majör depresyon tanılı kadınlarda dinamik tiyol/disülfid dengesinin antioksidatif bir reaksiyonu düşündürecek şekilde tiyol oluşumu yönünde olduğunu göstermiştir.* ***(Anadolu Psikiyatri Derg 2018; 19(2):135-142)***

Anahtar sözcükler: *Depresyon, oksidatif stres, kadın, tiyol, disülfid*

INTRODUCTION

Depression is a highly debilitating, multifactorial psychiatric disorder that is a global burden. It is thought that by the year 2020, depression will be the second leading cause of disability for people of all ages.[1] Epidemiological studies have shown that the lifetime prevalence of depression is 21.3% in women, which is almost twice that of men (12.7%).[2] In the last decade studies have investigated underlying neurobiological mechanisms of depression onset beyond the monoamine hypothesis. Recent studies have shown that depression is associated with oxidative stress and the dysregulation of antioxidant capacity.[3] Oxidative stress is implicated in the etiopathogenesis of several systemic diseases, including cardiovascular and neurodegenerative disorders, cancers, and metabolic conditions, such as diabetes and obesity.[4] Additionally, metabolic and cardiovascular comorbidities, which are associated with oxidative stress, are thought to be major causes of mortality in mood disorders.[5] Furthermore, oxidative stress has also been reported to be implicated in psychiatric conditions, including schizophrenia and attention deficit hyperactivity disorder.[6] Oxidative stress is a condition in which there is an imbalanced redox status caused by an excessive production of reactive oxygen species or an impaired antioxidant defense system, causing damage in particular neuronal cellular components.[7] Oxidative stress status is measured by several biochemical parameters, including free oxygen radicals and antioxidant enzyme activities.[8] As oxidative stress is considered to be associated with the initiation and progression of different systemic diseases caused by vascular endothelial dysfunctions, such as atherosclerosis, hypertension, and cardiovascular diseases, factors such as sex hormones and gender differences are thought to be associated with oxidative stress markers.[9-11] For instance, women have generally been reported to have less reactive oxygen species (ROS) and oxidative stress markers than males.[12] Additionally, the antioxidative effects of the female sex hormone estrogen is known to have an anti-inflammatory and endothelial protection role by modulating the release of protective enzymes.[9] In line with this data, several diseases associated with oxidative stress, such as cardiovascular diseases, malignancies, or neurodegenerative disorders have been found to be less prevalent in premenopausal women, in whom estrogen levels are highest, than in males and postmenopausal women.[9,13,14] However, though depression has been associated with oxidative stress and inflammatory processes, contrary to other aforementioned diseases, it has been shown that depression is more prevalent in women than men. Although some studies have investigated the differences on the markers of oxidant status and redox balance, there is currently not sufficient data to conclude a significant sex-specific oxidative stress biomarker.

Thiols are organosulfur compounds that have been shown to have an antioxidant function by several mechanisms, while dynamic disulphide bonds are thought to be associated with increased oxidative stress. Recent studies have shown that dynamic thiol/disulphide homeostasis reflects oxidative stress status and thus has been reported as a novel method for determining oxidative stress.[15] The use of this method has been shown to result in significant oxidative stress findings in several conditions, such as dementia and cardiovascular diseases.[16,17] Although some studies determined a relationship between oxidative stress and psychiatric diseases, to our knowledge, there are no studies on the relationship between dynamic thiol/disulphide homeostasis and depression. In light of the findings on sex differences in oxidative stress status and its related diseases, in this study, we aimed to investigate dynamic thiol/disulphide homeostasis in women with untreated major depression and determine whether there is a possible neurobiological relationship between oxidative stress and depression.

METHODS

In total, 54 female patients with untreated major depression and 68 healthy female controls were included in the study. During the enrollment of the study, all participants were questioned by

initial clinical assessment whether they had undergone any psychotropic treatment in the last three months. Only the participants who were medication-free for at least three months were included in study, while those receiving treatment for any medical condition were excluded. The study was conducted between December 2015 and May 2016. A psychiatric assessment was used to diagnose major depressive disorder in patients based on the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria. All participants were women between 18 and 65 years of age and in an ongoing clinical major depressive episode. Criteria that excluded patients from the study included comorbid psychiatric diagnoses; systemic or inflammatory disease, such as diabetes, cardiovascular disease, cancer rheumatic disease, ongoing medication, and depression with psychotic features. In the clinical assessment, a sociodemographic form, the Hamilton Anxiety Rating Scale (HAM-A), and the Hamilton Depression Rating Scale (HAM-D) were conducted on all included participants. The HAM-D is a psychometric tool that includes 17 items designed to measure the severity and symptoms of depression in adults.[18] Akdemir et al. conducted a study validating the efficacy of the Turkish version of the HAM-D.[19] The HAM-A is a 13-item rating scale that measures the severity and symptomatology of anxiety in adults.[20] Reliability and validity of the Turkish version of the HAM-A was reported by Yazıcı et al.[21] Fasting blood samples were collected from all participants to assess plasma thiol and disulphide levels. Written informed consent was obtained from each participant prior to their enrollment in the study. The study protocol was approved by the local Ethical Committee (Balıkesir University Faculty of Medicine Clinical Research Ethical Committee, Balıkesir, Turkey, Decision No. 2016/01, Date: 06.01.2016) and was conducted in accordance with the Declaration of Helsinki.

Serum samples were obtained by centrifuging the blood samples for ten minutes at 1500 x g before storing them at -80 °C until they were biochemically measured. After the plasma and serum separated, plasma thiols and disulphide levels were measured using a novel biochemical method developed by Erel and Neşelioğlu.15 Half of the difference between plasma native and total thiol levels ensured the dynamic disulphide quantity. After detecting the levels of plasma thiols and disulphide, the pairwise ratio of disulphide to native thiol, disulphide to total thiol, and native to total thiol were calculated.

Normality of variable distributions were assessed by the Kolmogorov-Smirnov test. Continuous variables with normal distributions are presented as mean±standard deviation, while those with abnormal distributions are presented as median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages. An independent t-test or Mann-Whitney U test were used to compare independent continuous variables when appropriate. Categorical variables were compared using a Chi-square or Fisher's exact test. To assess the correlation of data, Pearson correlation was used for normally distributed data, while Spearman's correlation was used for data that was not normally distributed. Statistical significance was set at $\alpha=0.05$.

RESULTS

A total of 54 patients and 68 healthy controls were evaluated in this study. There was no significant difference in age (p=0.30), marital status (p=0.83), education level (p=0.49),

Table 1. Sociodemographic data of patient and control groups

	Patient group (n=54)		Control group (n=68)		p
Age	34.5±11.7		36.8±12.2		0.30
Body Mass Index (BMI)	24.8±6.7		24.6±4		0.80
	n	%	n	%	
Smoking					0.11
Yes	16	29.6	12	17.6	
No	38	70.4	56	82.4	
Alcohol use					0.42
Yes	2	3.7	1	1.5	
No	52	96.3	67	98.5	

Table 2. Clinical and thiol/disulphide measurements of patient and control groups

	Patient group (n=54) Mean±SD	Control group (n=68) Mean±SD	t	p
HAM-D	20.8±3.7	3.0±2.6	30.7	<0.001
HAM-A	16.3±5.5	3.4±2.7	16.9	<0.001
Native thiol (µmol/L)	351.6±69.4	322.8±43.4	2.79	0.006
Total thiol(µmol/L)	368.8±70.1	351.3±46.3	1.65	0.10
Disulphide(µmol/L)	8.6±5.7	14.2±6.8	-4.87	<0.001
Pairwise ratios (%)				
Disulphide/native thiol	2.56±1.78	4.48±2.26	-5.08	<0.001
Disulphide/total thiol	2.39±1.54	4.04±1.86	-5.23	<0.001
Native thiol/total thiol	95.21±3.09	91.91±3.72	5.23	<0.001

HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale

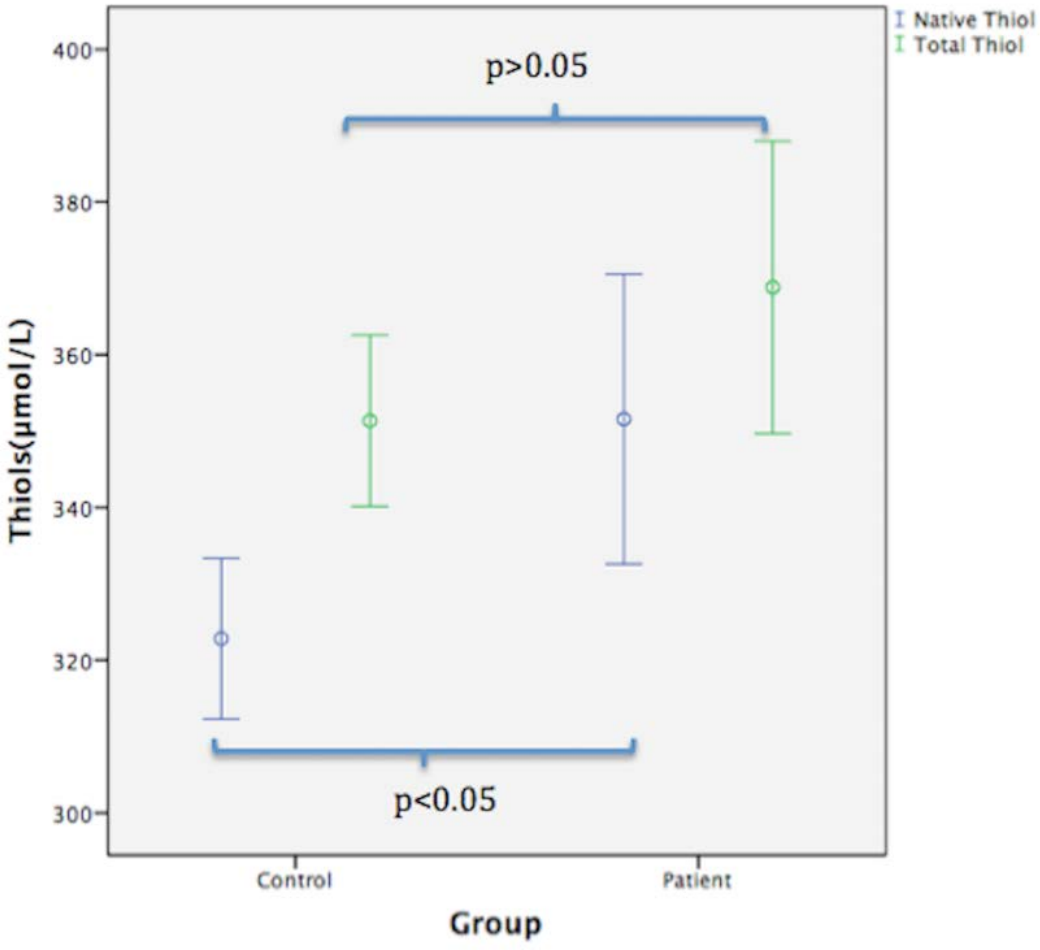

Figure 1. Distribution of serum thiols levels in patient and control groups

smoking status (p=0.11), or alcohol use (p=0.42) between the patient and control groups. The sociodemographic variables are shown in Table 1. The median duration of major depression was 5 (3-36, IQR) months. Thirty three patients (61.1%) were experiencing their first major depression episode, while 21 patients (38.9%) were in a second major depressive episode and had previously experienced an episode as confirmed by their medical history. As expected,

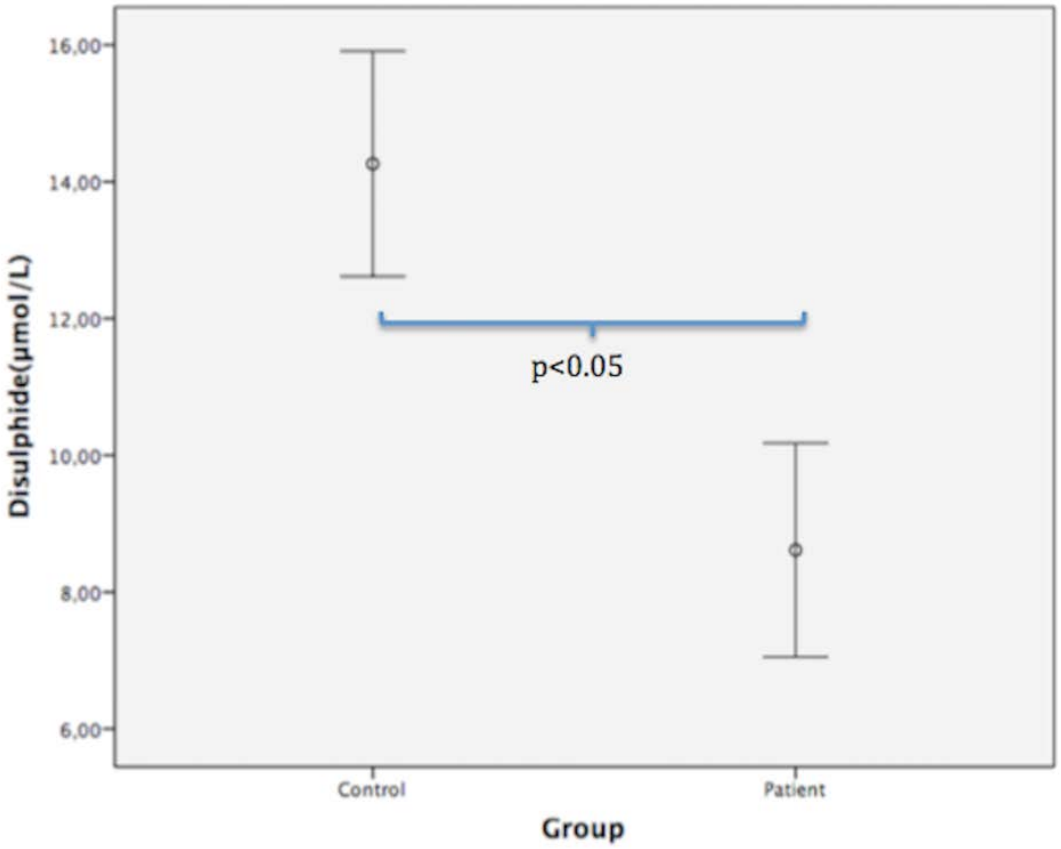

Figure 2. Distribution of serum disulphide levels in patient and control groups

HAM-D scores were significantly higher in patients as compared to controls (p<0.001) (Table 2). Additionally, HAM-A scores revealed that anxiety levels were also significantly higher in patients than controls (p<0.001) (Table 2). Plasma native thiol levels were higher in patients than controls (p=0.006), while plasma total thiol levels were not significantly different between groups (p=0.10) (Table 2, Figure 1). In the patient group, plasma disulphide levels were significantly lower than those in controls (p<0.001) (Table 2, Figure 2). Plasma disulphide and thiol ratio pairwise comparisons showed that the plasma disulphide/native thiol and disulphide/total thiol ratios were significantly lower (p<0.001), while the plasma native thiol/total thiol ratio was significantly higher in the patient group (p<0.001) (Table 2). When we compared plasma thiol/disulphide levels between first and second depressive episode patients, we found no significant difference (p>0.05). Through correlation analysis, we found that there was a negative correlation between HAM-D score and plasma disulphide level as well as plasma disulphide/native thiol ratio and plasma disulphide/total ratio, while there was a positive correlation between HAM-D score and plasma native/total thiol ratio in the patient group (Table 3). Plasma native thiol and total thiol levels in both the patient and control groups showed a negative correlation with age and BMI, while plasma disulphide/native thiol, disulphide/total thiol, and native thiol/total thiol ratios had a significant positive correlation with BMI in the patient group (Table 3). There was no significant correlation between the duration of major depression and plasma disulphide/thiol measures in the patient group. There was also no correlation between plasma disulphide/thiol measures and psychiatric clinical measures in the control group.

DISCUSSION

In our study, we investigate the relationship between depression and dynamic thiol/disulphide homeostasis in women. The results from this study showed that plasma native thiol levels were significantly higher, while plasma disulphide levels were significantly lower, in patients with major depressive disorder when compared

to healthy controls. Several studies have been conducted to investigate dynamic thiol/disulphide homeostasis in diseases associated with oxidative damage. A vast majority of these studies showed thiol/disulphide balance shifted toward disulphide formation under oxidative stress.[22] These results support that thiol/disulphide homeostasis shifts in favor of increased oxidative stress in inflammatory and/or oxidative diseases. In recent years, there have been some reports that support the idea that depression is an inflammatory disorder and the underlying neurobiological mechanism is associated with oxidative stress.[23] In addition, some studies have shown a decreased antioxidant capacity in patients with major depressive disorder.[24] Although thiol levels have been associated with antioxidant defense mechanisms and depression is reported to be related to oxidative stress,[23,25] our results showed that plasma thiol/disulphide homeostasis shifted in favor of the reductive side, thiol formation, in female patients with major depression. In addition to studies which support that depression is an inflammatory disorder accompanied by oxidative stress, there have been studies which also show increased thiol levels and total antioxidant status in patients with depression as compared to the healthy control population, consistent with our results.[25,26] Furthermore, in these studies, significant correlations between total antioxidant status, which involves increased thiol levels and decreased disulphide levels, and both cognitive decline as well as depression severity have also been reported.[26,27] As confirmed by numerous studies and literature, it is well known that thiols play a crucial role in defense through their sulphydryl (-SH) group that is involved in antioxidant mechanisms. Endogenous thiol levels can be altered as a result of oxidation by free oxygen radicals and can return to reversible disulphide bonds.[28,29] Although some studies have investigated thiol levels in depression, to our knowledge, no studies have extensively investigated dynamic thiol disulphide homeostasis, including not only thiol levels, but also disulphide levels, in women with major depression. In our study, plasma thiol/disulphide levels were determined by a novel method developed by Erel and Neşelioğlu. In their preliminary studies, they reported that increased thiol and decreased disulphide levels were associated with proliferated diseases, such as multiple myeloma and malignancies, whereas decreased thiol levels and increased disulphide levels were associated with degenerative diseases, such as diabetes, obesity, pneumonia and smoking.[30-32] However, our results showed that dynamic thiol disulphide homeostasis is associated with an increased shift to the reductive side as a proliferative manner, in women diagnosed with major depressive disorder. In our correlation analysis, we found a negative correlation between depression severity and plasma disulphide levels only in the patient group. This data supports the notion that plasma thiol/disulphide levels are prone to shift to the thiol form in female patients with major depression. These findings imply that although depression has been reported to be associated with increased oxidative stress, changes in dynamic thiol disulphide homeostasis, at least in women, are associated with increased shift to the reductive side. This data implies that in a depression model, dynamic thiol/disulphide homeostasis may be involved in compensatory mechanisms of oxidative stress burden which results in a shift in favor of the thiol.

Previous studies that investigated the relationship between age, obesity, oxidative status, and inflammation have reported that decreased thiol levels, which reflects decreased antioxidant capacity, is associated with increased age and adiposity.[33,34] In our study, both the patient and control groups had negative correlations between age, BMI, and plasma thiol levels. In the patient group, there was a positive correlation between BMI and plasma disulphide/thiol pairwise ratios. These results were consistent with previous reports that demonstrated decreased antioxidant capacity with age and adiposity.

There are some limitations that should be considered in the interpretation of our study. First, although dynamic thiol/disulphide homeostasis reflects oxidative state, depression is a condition mainly associated with the central nervous system. Hence, peripheral measurements of thiol and disulphide levels may not be sufficient to conclude the oxidative status of the central nervous system. Second, our samples were solely from the female population. Although our homogenous study population in terms of gender may yield relatively more precise results, in our study there is a prominent lack of data regarding dynamic thiol/disulphide homeostasis in the male population diagnosed with major depressive disorder. Lastly, our sample size was relatively small to make a conclusion regarding dynamic thiol/disulphide homeostasis in major depressive disorder.

In conclusion, to the best of our knowledge, this is the first study to comprehensively investigate dynamic thiol/disulphide homeostasis in major

depressive disorder. We found increased plasma native thiol levels and decreased plasma disulphide levels in a population of women diagnosed with major depressive disorder as compared to healthy controls, while there was a negative correlation between plasma disulphide levels, disulphide/thiol ratios, and depression severity. Our results support the notion that although oxidative stress has been reported to be increased in depression, oxidative stress pathways, such as dynamic thiol/disulphide homeostasis, may be complicated in women with major depression. Contrary to other reported systemic diseases, in the female population, dynamic thiol/disulphide homeostasis may be associated with different mechanisms, such as increased anti-oxidative compensations as a response to depression in oxidative stress. Furthermore, we believe that our results not only contribute to data regarding oxidative stress domains of depression, but also highlight the significance of biological pathways as well as the complicated nature of depression models. Future studies with larger sample sizes are warranted to determine whether there is a relationship between major depressive disorder and oxidative stress markers, including dynamic thiol/disulphide homeostasis.

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