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Evaluation of Thiol/Disulfide Interrelation in Major Depressive Disorder

ABSTRACT

Objective: Although major depressive disorder (MDD) constitutes a significant part of mental health problems, its pathogenesis has not been fully elucidated. The inadequacy of diagnostic tests specific to MDD causes difficulty in diagnosis. Therefore, we investigated the situation of thiol/disulfide imbalance, which may play a role in the pathogenesis of many diseases, in MDD patients.

Methods: Forty-five MDD patients and 40 non-patient volunteers participated in our study. Sociodemographic data form, Beck Depression Scale, and Clinical Global Impression Scale were used in making the diagnosis and evaluation process.

Results: There was a significant difference between the MDD and non-patient groups in native thiol and total thiol levels, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios. No significant difference was detected in terms of disulfide level between the 2 groups. There was no significant difference between the patients' thiol disulfide ratios and the severity of depression. There was no significant difference between the patients' symptom duration and thiol disulfide ratios. Nevertheless, a negative correlation was identified between the duration of the patients' symptoms and their disulfide levels.

Conclusion: When the results were examined in terms of thiol and disulfide ratios, they showed that thiol and disulfide ratios were impaired in depression. We think that thiol/disulfide parameters may be a biomarker candidate that can help in the diagnosis of MDD.

Keywords: Disulfide, dynamic thiol/disulfide balance, major depressive disorder, oxidative stress, thiol

Introduction

Major depressive disorder (MDD) is one of the areas of intensive study of clinicians working in psychiatry practice.[1] Major depressive disorder is the most common psychiatric disorder, and the risk of developing it is 16.2%; this figure is even higher if disorders within the depressive spectrum are also taken into account.[2,3] Major depressive disorder is more common in women than in men.[4] The probability of its development throughout life varies between 10% and 25% in women and 5% and 12% in men.[4,5] Major depressive disorder is an important factor for completed suicides.[6,7]

The effects of free radicals that occur in normal metabolism or through pathological intracellular and extracellular events are called oxidative stress.[8] Recent investigations have explored the connection between elevated oxidative stress and the development of various conditions, including schizophrenia, bipolar disorder, major depressive disorder, obsessive-compulsive disorder, and generalized anxiety disorder.[9,10,11] There are antioxidant systems in the body that act as protection against free radical damage at various stages, and these systems are affected by disrupted body balance and by oxidative stress caused by free radicals.[12]

Various compounds protect against oxidative stress, one of which is the thiol group. Organic compounds with thiol groups play a significant role in protecting against oxidative

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stress due to their reducing properties.[13] Thiols undergo oxidation when exposed to oxidizing molecules in the environment, leading to the formation of reversible structures with disulfide linkages. The resultant structures with disulfide linkages can be reversed to thiol groups, thus preserving the thiol/disulfide equilibrium.[14] Antioxidants, particularly thiol groups, which aim to counteract the detrimental impacts of free radicals, struggle to sustain their concentrations in plasma and tissues in the face of these damaging effects.[12]

Recent research has indicated that reactive oxygen radicals might contribute to the pathophysiology of depression by inducing neuronal damage due to an imbalance between oxidative and antioxidative systems.[15-16,17] The current research was devised to assess thiol/disulfide parameters in individuals with MDD, a condition where oxidative stress is understood to be a factor, and to determine if these molecules, measurable in clinical settings, could serve as a distinctive marker.

Material and Methods

Subjects

The subjects of the study were: (1) 45 patients diagnosed with MDD who applied to the psychiatry outpatient clinic of Harran University Faculty of Medicine Training and Research Hospital between June 2016 and December 2016 and (2) 40 healthy volunteers. All participants provided informed consent. The study received approval from the Harran University Clinical Research Ethics Committee (Approval No: 07, Date: January 25, 2016).

The individuals taking part in our study fulfilled the diagnostic criteria for MDD in accordance with the DSM-V guidelines, were in the attack phase of MDD, and had the mental capacity to give consent. They had not undergone any psychiatric treatment within the preceding 3 months, had not received any medication in the previous week, and did not have comorbid psychiatric conditions. The final group consisted of 45 MDD patients who did not have any disorders or physical diseases, were not pregnant or lactating, were not smokers, and willingly agreed to take part in the study.

Procedures

The patients underwent a routine psychiatric examination and took the Beck Depression Scale and Clinical Global Impression Scale questionnaires. Then, blood was drawn from each patient.

The blood was placed into ethylenediaminetetraacetic acid biochemistry tubes and centrifuged. The resulting sera was placed in a −80°C freezer in the Clinical Biochemistry Laboratory of Harran University Faculty of Medicine.

MAIN POINTS

- *Oxidative stress and the related thiol-disulfide balance have an impact on the development of major depressive disorder (MDD).*
- *There was a significant difference in some measurable parameters of thiol disulfide balance in patients with MDD compared to those in the control group.*
- *We found that there was a negative correlation between disease duration and thiol disulfide balance in some parameters in the patient group.*

After the collection of samples was completed, the thiol/disulfide balance was assayed using the automatic measurement method of Erel and Neselioglu.[18] Dynamic disulfide bonds were converted into free thiol groups through the use of sodium borohydride. Any remaining reductants that went unused were effectively eliminated by employing formaldehyde to ensure an accurate determination of the total thiol content. Natural thiol groups were assessed using a modified Ellman reagent. The number of disulfide bonds was calculated by taking half of the difference between the total thiol and native thiol quantities. Subsequently, the ratios of disulfide/total thiol, disulfide/native thiol, and natural thiol/total thiol were computed. To assess thiol-disulfide homeostasis, serum and plasma samples were used, following the established methodology from previous research articles.

Results

Our research groups consisted of 45 patients and 40 healthy volunteers. The age range in the MDD group was 18-62, with the average being 30. Of the 45 patients, 34 were women and 11 were men. In the MDD group, 16 were single, 24 were married, 4 were divorced, and 1 was widowed. While 27 of the patient group were unemployed, 18 were working in various jobs. The age range of the volunteer group was 20-70 years old, and the average was 32 years. Of the 40 volunteers, 32 were women and 8 were men. Of the volunteer group, 12 were single, 20 were married, 3 were divorced, and 5 were widowed. While 26 of the volunteer group were unemployed, 14 were working in various jobs. The sociodemographic characteristics of both the depression and volunteer groups are presented in Table 1. There was no significant difference between the MDD and volunteer groups in terms of age, gender, and body mass index (BMI). The BMI of the patient group was 23.9 $\pm$ 3.20, and the BMI of the volunteer group was 25.04 $\pm$ 3.80. This situation is shown in Table 2.

We examined previous treatment history, inpatient treatment history, family history, suicide attempt, possible disease duration, and viral preservation status, as shown in Table 3. We observed that 8 (17.8%) had received treatment previously, and 37 (82.2%) had no previous treatment history. One of the patients who had previously received treatment was receiving inpatient treatment. Regarding the family history of the patients, 38 (84.4%) did not have any psychiatric disorders in their families; 4 (8.9%) had a family history of depression; 1 (2.2%) had a family history of bipolar disorder; 1 (2.2%) had a family history of anxiety disorder; and 1 (2.2%) family member had a psychotic disorder. In the study, only 1 patient, which accounted for 2.2% of the total patients included, had reported a suicide attempt. In regard to the duration of the patients' illness, 6 patients (13.3%) had complaints for 1 month, 6 (13.3%) had complaints for between 1 and 3 months, 12 (26.7%) had complaints for between 4 and 6 months, 6 (13.3%) had complaints for between 7 and 12 months, and 15 patients (33.3%) had complaints for more than a year. According to the Beck depression scale administered to the patients, the depression of 5 patients (11.1%) was evaluated as mild, 29 patients (64.4%) as moderate, and 11 patients (24.4%) as severe. None of the patients included in the study had received Electroconvulsive therapy (ECT) treatment.

The table in Table 4 presents a comparison between the total thiol, native thiol, and disulfide levels, as well as the ratios of disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol for both the depression group and the healthy control group.

Table 1. Sociodemographic Data of the Depression Group and Volunteer Group

	Depression Group	Volunteer Group
Age		
Average (minimum–maximum)	30 (18-62)	32 (20-70)
Gender (%)		
Women	34 (75.5)	32 (80)
Men	11 (24.5)	8 (20)
Marital status (%)		
Single	16 (35.6)	12 (30)
Married	24 (53.3)	20 (50)
Divorced	4 (8.9)	3 (7.5)
Widow	1 (2.2)	5 (12.5)
Job (%)		
Unemployed/Housewives	27 (60)	26 (65)
Self-employed	7 (15.6)	5 (12.5)
Civil servants	3 (6.7)	3 (7.5)
Worker	1 (2.2)	2 (5)
Student	7 (15.6)	4 (10)
Education status		
Uneducated	12 (26.7)	13 (32.5)
Primary school graduates	9 (20)	8 (20)
Secondary school graduates	7 (15.6)	8 (20)
High school graduates	8 (17.8)	6 (15)
College graduates	9 (20)	5 (12.5)

When the depression group and the control group were compared for native thiol and total thiol levels and native thiol/total thiol ratios, the depression group levels were found to be significantly lower, as seen in Table 4. The disulfide/native thiol and disulfide/total thiol ratios were significantly higher in the depression group than in the control group. There were no significant differences between the groups in disulfide levels.

As seen in Table 5, no significant relationship was found between the patients' depression severity (assessed by the Beck depression scale) and total thiol, native thiol, or disulfide levels, or disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ratios ($P > .05$). No correlation was found between the duration of the patients' symptoms and total thiol and native thiol levels ($P > .05$).

We observed a notable negative correlation between the duration of the patients' symptoms and the ratios of disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol ($P = .034$).

Discussion

In the existing body of literature, limited research has been conducted to explore the correlation between oxidative stress and the antioxidant system in psychiatric disorders or to analyze the relationship of thiol/disulfide balance to psychiatric disorders. At the time we started our study, to our knowledge, no study investigating the thiol/disulfide balance in depression had been conducted.

Research provides evidence supporting the connection between oxidative stress and impairments in neurogenesis and synaptic plasticity in depression, primarily by associating these factors with brain derived neurotrophic factor. A recent study emphasized that the diminished levels of neurogenesis observed in mice with stress-induced depression were restored by increasing the expression of the mitochondrial antioxidant sirtuin 3. This approach holds promise as a strategy to enhance stress resilience and ameliorate depressive behavior.[19]

In the present study, native thiol and total thiol levels, used as antioxidant levels, and the native thiol/total thiol ratio, used as an

Table 2. Assessment of Gender, Age, and Body Mass Index in Relation to the Comparison Between the Depression and Control Groups

	Depression Group	Volunteer Group	*P*
Gender (W/M)	34/11	25/15	.192
Age (average) (minimum–maximum)	30 (18-62)	37.5 (20-70)	.176
Body mass Index	23.9 ± 3.20	25.04 ± 3.80	.170

Table 3. Clinical Features of the Patients

Parameters	Number of Patients	%
Previous treatment history		
Yes	8	17.8
No	37	82.2
Inpatient treatment		
Yes	1	2.2
No	44	97.8
Family history		
Absent	38	84.4
Depression	4	8.9
Bipolar disorder	1	2.2
Anxiety disorder	1	2.2
Psychotic disorder	1	2.2
Suicide attempt		
Yes	1	2.2
No	44	97.8
Disease duration		
1 month	6	13.3
1-3 months	6	13.3
4-6 months	12	26.7
7-12 months	6	13.3
Longer than 1 year	15	33.3
Depression severity		
Mild	5	11.1
Moderate	29	64.4
Severe	11	24.4

Table 4. Comparison of Depression Group and Control Group in Thiol/Disulfide Balance

	Depression Group	Volunteer Group	*P*
Native thiol*	333.6 ± 107.5	402.9 ± 62.8	.016
Total thiol**	420.2 (105-686.5)	441.2 (303.6-614.9)	<.001
Disulfide	21.5 ± 7.08	19.1 ± 5.44	.171
Disulfide/native thiol**	6.31 (2.31-35.5)	4.40 (2.62-9.85)	.002
Disulfide/total thiol**	5.60 (2.20-20.7)	4.04 (2.49-8.23)	.002
Native thiol /total thiol**	88.7 (58.4-95.5)	91.9 (83.5-95.0)	.002

*Mean (SD).
**Median (minimum–maximum).

Table 5. Examination of Depression Severity and Disease Duration in Relation to Thiol/Disulfide Balance

	Beck Score	Native Thiol	Total Thiol	Disulfide	Disulfide/ Native Thiol	Disulfide/ Total Thiol	Native Thiol/ Total Thiol
Depression severity							
R value	1	0.192	0.172	−0.023	−0.052	−0.052	−0.052
P		.196	.246	.876	.730	.730	.730
Duration							
R değeri	1	0.045	0.018	−0.310	−0.237	−0.237	−0.237
P değeri		.762	.762	.903	.034	.034	.034

antioxidant level, were found to be significantly lower in depressed patients, whereas disulfide/native thiol and disulfide/total thiol ratios, which are indicators of increased oxidation, were found to be significantly higher in depressed patients. Finally, no correlation was found between the severity of the disorder and oxidation parameters, but a negative correlation was found between the duration of symptoms and disulfide levels.

While we were running the present study, a study was published that examined the thiol/disulfide-balance parameters of oxidative stress in unipolar depression patients, both with and without mixed symptoms. The disulfide level, total thiol, oxidation–reduction rate, and oxidized thiol levels, which are all indicators of increased oxidation, were significantly higher in the unipolar depression group than in the control group. The level of reduced thiol, which is an indicator of the antioxidant system, was found to be significantly lower in the unipolar group than in the control group. No significant differences were detected between the depression-with-mixed-symptoms group and the depression-without-mixed-symptoms group in oxidative stress parameters.[20]

We found one study, conducted with 87 patients diagnosed with schizophrenia, in which a significant difference was observed between the patient group and the control group in thiol/disulfide balance. In that study, native thiol and total thiol levels were found to be lower than in the control group, and disulfide levels were higher.[21]

In a study comparing patients in both the manic and remission periods of bipolar disorder with a control group, thiol and disulfide ratios were examined; thiol levels of patients in the manic period and the remission period were found to be significantly lower than those in the control group, and no significant difference was detected between the manic and remission periods. The authors reported that there was no significant difference in disulfide levels among the 3 groups. It has been speculated that the thiol-disulfide imbalance in bipolar disorder may be a permanent change and may not differ according to the stages of bipolar disorder.[10] In another study comparing the manic period of bipolar disorder with the remission period, native thiol levels, which are indicators of antioxidant capacity, were found to be lower in patients in the manic period than in those in the remission period. In the same study, no difference was found in total thiol values between the 2 groups.[22] In another study, 40 panic attack patients had lower thiol levels than did the control group; disulfide/total thiol ratios were found to be higher in the panic attack group than in the control group.[23]

In a study investigating the dynamic thiol disulfide balance in patients diagnosed with generalized anxiety disorder (GAD) and panic disorder (PD) who were not under medication, it was observed that untreated GAD and PD patients had notably lower natural thiol levels and natural thiol/total thiol ratios compared to those in the control group. Additionally, the levels of disulfides and disulfide/native thiol ratios were significantly higher in these patients in comparison to the control group. On the other hand, no significant difference was detected between the groups in thiol and disulfide levels among any GAD or PD patients.[24]

In a previous study that we conducted in our clinic on 120 patients diagnosed with GAD, we found that dynamic disulfide levels and ratios of disulfide/natural thiol and disulfide/total thiol were higher in untreated GAD patients than in the controls, but there was no significant difference in total thiol and natural thiol levels between GAD patients and healthy subjects. We additionally found that the native thiol/total thiol ratio was significantly lower in untreated GAD patients than in the control group.[25]

A study on childhood attention-deficit hyperactivity disorder (ADHD) found no significant relationship between dynamic thiol/disulfide balance and ADHD.[26]

In a study on epilepsy patients, no significant difference was found between total thiol and native thiol or dynamic disulfide bond levels between epilepsy patients and healthy volunteers.[27]

A possible increase in the levels of oxidative stress markers in major depression and a decrease in antioxidant status with major depressive symptoms,[28] suggest that reactive oxygen radicals play a role in the pathophysiology of depression by causing neuronal damage as a result of the disruption of the balance between oxidative and antioxidative systems.[15-16] The majority of studies on oxidant/antioxidant balance and antioxidant levels in psychiatric disorders, including our study, support these previous studies and suggest that antioxidant levels decrease and the oxidant/antioxidant balance is disrupted in depression.

The limitations of our study include the fact that the sample group was relatively small, most of the patients were women, it was a cross-sectional study, the patient group did not have a first attack, and they had used psychotropic drugs in the past.

Biological factors play a role in major depressive disorder. Although significant advances have been made in this field, there are still no biological markers that can directly contribute to the diagnosis.

Thiol/disulfide balance has been studied in some psychiatric disorders; in the present study, which is the first conducted in MDD patients, we found that the thiol/disulfide balance is disrupted in depression. We found that there is no correlation between the

severity of the disease and the thiol/disulfide balance but that there is a correlation between the duration of the symptoms and some, but not all, of the thiol/disulfide-balance parameters.

Consequently, it can be inferred that thiol/disulfide balance parameters may serve as potential candidates for biological markers that could be employed in the diagnosis of depression.

Data Availability Statement: *The data that support the findings of this study are available from the corresponding author upon reasonable request.*

Ethics Committee Approval: *The study received approval from the Harran University Clinical Research Ethics Committee (Approval No: 07, Date: January 25, 2016).*

Informed Consent: *Written informed consent was obtained from the participants who agreed to take part in the study.*

Peer-review: *Externally peer-reviewed.*

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