


Investigating the Impact of the ECT on Thiol-Disulphide Homeostasis in Depressive Disorders

Murat Ilhan Atagun ^a , Ozge Canbek Atay ^b , Ozlem Balaban ^b , Derya Ipekcioglu ^b , Baris Alpugan ^b ,
Suat Yalcin ^b , Almila Senat ^c , Nesrin Karamustafalioglu ^b , Mehmet Cem Ilnem ^b , Ozcan Erel ^c 

^aDepartment of Psychiatry, Ankara Yildirim Beyazit University Medical School, ^bDepartment of Psychiatry, Istanbul Bakirkoy Research and Treatment Hospital for Psychiatry, ^cDepartment of Medical Biochemistry, Ankara Yildirim Beyazit University Medical School

Abstract

Background: Depressive disorders are characterized by oxidative stress and burden of oxidative stress may provoke cellular and biochemical challenges. Thiols are converted into non-reactive disulphides after reacting with oxygen radicals and converted back to thiols. N-terminus of the albumin can be modified by biochemical strain and modified albumin is called ischemia modified albumin (IMA). In this study, it was aimed to assess potential effects of electroconvulsive therapy (ECT) on thiol disulphide homeostasis and IMA levels in depression.

Methods: Twenty-three patients with depressive episodes (major depressive disorder n=16), and (bipolar disorder n=7) and 21 healthy controls were enrolled. Serum samples were collected at three time points: one day before ECT, one hour after the first ECT session and one hour after the last session (remission). Thiol disulphide homeostasis and IMA levels were measured.

Results: Total thiol levels were significantly ($p=0.032$), native thiol levels were trend level ($p=0.056$) depleted in patients with depression in comparison to that of the healthy control group. Disulphide levels did not differ between the groups. IMA levels were higher ($p<0.001$) in the patient group initially. Thiol disulphide or IMA levels did not significantly change in the depression group after the first and last ECT sessions.

Conclusion: Although previous studies have reported favorable effects of ECT on various oxidative stress markers, ECT did not influence thiol disulphide or IMA levels in the patient group. These findings provide biochemical support for the safety and efficacy of ECT at subcellular level.

ARTICLE HISTORY

Received: Apr 19, 2020

Accepted: May 15, 2020

KEYWORDS: depressive disorders, thiol, disulphide, electroconvulsive therapy

INTRODUCTION

Depressive disorders (DD) are extremely common mental disorders, with a lifetime prevalence of 18.4% [1]. Although DD induce chemical and endocrine alterations [2, 3], their etiopathogenesis remains to be elucidated yet. Volumetric brain imaging studies have consistently shown volumetric loss in hippocampus and prefrontal cortex in depressed patients [4]. Neuronal size and density as well as glial cell number and density have been shown to be reduced [5, 6]. Acute ischemia, physical trauma, infections, inflammation, oxidative stress, acidosis/alkalosis, electrolyte imbalances, metabolic syndrome, extreme temperature changes, high voltage electric currents may cause biochemical abnormalities that may result in cellular insult. Due to increased production of free radicals, oxidative stress is one of the most important causes of the neuronal alterations in DD [7-9]. Oxidative

stress is defined as imbalance between free radicals and anti-oxidant defenses, which results in increased reactive oxygen species. The brain is under more severe risk for oxidative stress, because of its high metabolic rate and high density of fatty acids and metal ions which are notable electron donors [10]. Increased oxidative stress may induce cellular dysfunction and apoptosis by causing lipid peroxidation, breaks in DNA strand, protein/enzyme inactivation, and disrupt cellular signaling cascades in the brain [10].

Sistine residues and sulfhydryl groups are functional groups of amino-acids which are also called thiols [11]. Thiols are reductive organic compounds and turn into non-reactive disulphides such as sulphinic acid or thiol radicals if they react with reactive oxygen radicals. Disulphides are later converted to thiols by reductants such as thioredoxin,

Corresponding author: Murat Ilhan Atagun, E-Mail: miatagun@ybu.edu.tr

To cite this article: Atagun MI, Atay Canberk O, Balaban O, Ipekcioglu D, Alpugan B, Suat Yalcin, Senat A, Karamustafalioglu N, Ilnem MC, Ozcan Erel O. Investigating the Impact of the ECT on Thiol-Disulphide Homeostasis in Depressive Disorders. Psychiatry and Clinical Psychopharmacology 2020;30(2):1-8, DOI: 10.5455/PCP.20200419045142

glutaredoxin and thiol-disulphide homeostasis is hereby maintained [11]. Several proteins such as albumin, sistein, homo-sistein, glutathione, gamma-glutamyl sistein may contain thiol components and free thiols may also circulate in plasma [12]. Several metabolic procedures are involved with thiol groups such as anti-oxidant defense, protein synthesis, cell proliferation and growth, signal transmission, apoptosis and immune regulation [11]. Erel and Neşelioğlu have developed a new fully-automated assay to evaluate dynamic thiol-disulphide homeostasis [13]. Thiol groups participate in the first line defense against oxidative stress, thus dynamic thiol-disulphide homeostasis has been investigated in several psychiatric disorders [14-17]. Thiol-disulphide homeostasis was also assessed in patients with major depressive disorder and the authors reported that serum level of thiols were depleted [18].

Human albumin is a protein with 585 amino-acids, which contain 35 cysteine residues. The only free cysteine residue at position 34 (cys34) holds a free thiol group (-SH) accounting for 80 % of thiol groups in the plasma [19]. One of the most important function of albumin is to bind molecules in the blood stream. Chemical configuration of the last 4 amino-acids forms a specialized structure for the N-terminal which enables albumin to bind transitional metals such as cobalt or iron [20, 21]. This function is disabled when the unique chemical structure of the N-terminus is altered. This phenomenon is called ischemia modified albumin (IMA), because the first observations were in cases of hypoxia and acidosis [20]. Later, it became evident that N-terminus of the albumin can become modified by several medical cases causing biochemical stress such as extreme changes in temperature, disturbed acid-base balance, metabolic syndrome, inflammation or oxidative stress [22]. In a recent study, it has been reported that IMA levels in remitted patients with recurrent depressive disorder were not significantly different from that of healthy controls [22]. However, to our knowledge no studies have up to date evaluated the effects of ECT on IMA levels in patients with DD. Induction and seizure steps of the ECT may cause modification of the N-terminus of the albumin molecule.

Electroconvulsive therapy is an effective treatment modality for DD and in particular for treatment resistant depression [23]. A number of studies have reported that the ECT has positive impact on neurotransmitters [24] as well as immune [25-28] and endocrine [27, 29, 30] systems. Only few studies assessed the effects of ECT on oxidative stress markers and consistently reported that ECT alleviated oxidative stress [31-34]. However, to our knowledge, up to date no studies assessed the effects of ECT on thiol disulphide homeostasis. Repetitive transcranial magnetic stimulation decreased serum levels of native and total thiols [35]. In this study we aimed to investigate serum thiol disulphide homeostasis in patients with DD and potential effects of the ECT. Thiol pools are regulated by mechanisms linked to their intrinsic reactivity against antioxidants, thiol-disulphide exchange rates and their dynamic release/removal from plasma. The ECT may reorganize the thiol pool by altering chemical reactions. To our knowledge, this is the first study to assess

the effects of ECT on thiol disulphide exchange in DD.

METHODS

Local ethical committee approval was obtained for the study. All participants provided a written informed consent before study participation. Consecutive inpatients with depressive episodes (either Major Depressive Disorder or Bipolar Disorder) who were planned to be treated with ECT (decisions were made by independent senior physicians) were invited to participate in the study. Diagnoses were checked with structured clinical interview for DSM-IV (SCID-I) by a senior psychiatrist [36, 37]. Patients and healthy control subjects were evaluated according to the inclusion and exclusion criteria. Participation to the study was offered to the patients with an accompanying first-degree relative. Patients who accepted to participate were enrolled. Participants were between the age of 21-61. Medical and psychiatric history were checked in terms of exclusion criteria. The exclusion criteria were any medical comorbidities (systemic or neurological diseases), psychiatric comorbidities, history of major surgeries (brain, cardiac, thoracic or abdominal surgery), any infectious diseases in the preceding month, nutritional deficiencies and rapid reduction in weight. Totally 23 patients were enrolled into the depression group. A healthy control group (n=21) was also recruited. Healthy controls (HCs) were examined with the SCID nonpatient form. Exclusion criteria for HCs were history of substance and alcohol use disorder, cranial injury, major surgery, any infectious disease in the last month.

Hamilton Depression Rating Scale (HDRS): The HDRS has been the gold standard for the assessment of depression for almost 50 years. It is developed by Hamilton in 1960 [38] and translated into Turkish by Akdemir and colleagues [39]. 17, 21 and 24 item versions are available, the original 17 item version is the most frequently used version. Test retest reliability of the Turkish version was coefficient was 0.85, interrater reliability was ranging between 0.87-0.98 and the coefficients show that Turkish version of the scale has good reliability and validity measures [39]. The scale is administered by clinicians.

Brief Psychiatric Rating Scale (BPRS): Developed by Overall and Gorham, using factor analysis [40]. Interrater reliability ranges from 0.67 to 0.95; and reliability ($p < 0.01$) and validity ($p < 0.01$) measures were high in patients with schizophrenia [41]. Five items are based on clinician's observations (tension, emotional withdrawal, mannerism-posturing, motor retardation and uncooperativeness) and the other 13 items are assessed by patient's verbal cooperation. Items are Likert type rated on a 7 points scale, 1 not present and 7 extremely severe. By summing the item scores, a total score is obtained which can vary between the range of 18-126 points.

Clinical Global Impression (CGI): The CGI is designed to assess global severity of illness and change in the clinical condition over time. The scale provides an overall

summary measure that evaluates all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. It consists of 3 global subscales: Severity of Illness; Global Improvement; Efficacy Index. Item 1 is rated on a seven-point scale (1=normal to 7=extremely ill); item 2 on a seven-point scale (1=very much improved to 7=very much worse); and item 3 on a four-point scale (from none to outweighs therapeutic effect).

The decision of ECT was made by the patients' attending psychiatrists. A written informed consent was obtained from the patient or a first-degree relative before the administration. Electroconvulsive therapy (ECT) sessions were performed in the ECT unit of the hospital, between 08.00 - 11:00 in the morning. ECT applications of the hospital are all performed in an equipped unit for anesthesia procedures of the hospital [42-44]. The ECT unit was fully equipped with the devices needed for ECT applications under anesthesia and life supporting systems such as ventilators, respirators, defibrillator, electrocardiogram (ECG). According to the routine ECT procedures, all patients were controlled with laboratory tests including hemogram, liver, kidney and thyroid function tests. Patients were on fasting for 12 hours prior to ECT sessions. Blood pressure, ECG and oxygen saturation were monitored. A pulse oximeter (Nonin 2500A pulse oximeter) placed on the index finger monitored the vital signs. Succinylcholine (0.5 mg/kg) and Propofol (0.75-1 mg/kg) were administered as anesthetic medications. Before electrical stimulation patients had ventilation support with an airway, ambu mask and bag. During the electrical stimulation and convulsive phase, dental arches were protected with a sponge. A brief-pulse square-wave ECT device (Thymatron System IV ECT; Somatics, Inc., Lake Bluff, IL, USA) was used. ECT applications were bilateral fronto-temporal. Initial electrical stimulus charge energy was set by the doctor according to the half-age criteria and other influential factors such as concomitant pharmacotherapy, age, gender, prior to the ECT treatment. Seizures were considered as effective if they lasted more than 25 seconds. All patients were under intense medical care until complete recovery (30-60 minutes).

Blood samples were obtained from antecubital veins, at 08:00-12:00 am. All participants were controlled to be on 12 hours of fasting. Three samples were collected from each patient at different time points: prior to the first ECT session [first], after the first session [second] and after the last session [third]. Blood samples were obtained 30 minutes after the ECT sessions. The blood samples were left for 30 minutes at room temperature (22 °C) to activate clotting process followed by centrifuges at 1500 g x15 minutes. Serum samples were aliquoted and kept at - 80 °C freezer. Samples were transferred to the biochemistry laboratory for analyses.

Serum thiol/disulphide homeostasis parameters were measured according to Erel and Neselioglu method [13]. Briefly, disulphide bonds in serum were reduced with

sodium borohydride to form free thiol groups and unused sodium borohydride was removed with formaldehyde. After that, native (-SH) and reduced thiol (-SH and -SS) groups were determined by using reaction with 5,5'-dithiobis-(2-nitrobenzoic acid). Serum disulphide levels (-SS) were calculated via half of the difference between the total thiols and native thiols. Native thiol, total thiol and disulphide amounts (SS), disulphide/total thiol percent ratios (SS/SH+SS), disulfide/native thiol percent ratios (SS/SH) and native thiol/ total thiol percent ratios (SH/SH+SS) were calculated. These results are presented as micromole/liter (*mmol/L*), ratio and percentage.

Serum albumin levels were evaluated with bromocresol green (BCG) method and IMA levels were detected by the method described by Bar-Or and colleagues [21]. This manual colorimetric assay measures exogenous cobalt (Co²⁺) binding facility of the serum albumin. 50 µL water with % 0.1 cobalt chloride (CoCl₂.6H₂O) solution was mixed with serum (200 µL) and leaved in a dark room for ten minutes. Moreover, 50 µL dithiothreitol solution with 1.5 mg/mL H₂O was added to the serum and placed for two minutes. In order to trim the reaction, % 0.9 NaCl was also added to the solution. The blank was laid just as the exclusion of dithiothreitol. Absorbencies of the specimens were evaluated with spectrophotometer at 470 nm. IMA concentrations were obtained by measuring the difference between the samples with and without dithiothreitol. IMA levels are measured as absorbance units (ABSU).

Statistical Analyses

Statistical analyses were performed with SPSS 21 (IBM incorporation, New York, USA) software. Continuous variables are reported with means and standard deviations or medians and percentiles. Categorical variables are reported with frequencies and percentages. Continuous variables were checked with Shapiro Wilk Test for their distribution characteristics. Parametric tests were picked for normally distributed variables and non-parametric tests were chosen for skewed variables. The groups were compared to determine whether there is any statistical difference between the groups in any variables. In the first step, patients with DD were compared with the HC group and for two group comparison t test or Mann Whitney U Test were selected. In the second step, levels of biochemical variables were compared within the DD at the beginning, after the first session and after the third session. Three time points were compared with Analysis of Variance (ANOVA) or Kruskal Wallis Test [32]. Categorical variables such as gender or marital status were analyzed with Chi-Square Test. Correlations between the variables were performed with Spearman's Rank Correlation Test. Analysis of covariance (ANCOVA) is a test to examine the differences in the mean values of the dependent variables that are related to the effect of the controlled independent variables while taking into account the influence of the uncontrolled independent variables. Potential covariance effects were assessed with univariate ANCOVA test. Logarithmic transformation was applied to the deviated variables (Native Thiol and Total

Thiol) to meet the assumptions of the univariate ANCOVA. Level of statistical significance was set as $p < 0.05$. All tests results were two-tailed.

RESULTS

Sociodemographic and clinical variables of the participants are presented in Table 1. The study enrolled 23 patients with DD (7 bipolar disorder, depressive episode; 16 major depressive disorder episode) and 21 healthy control subjects. Genders were matched between the groups, however there were difference between age ($p = 0.022$) and education ($p < 0.001$). 12 of the patients were treated with ECT because of medical emergency (severe suicide risk, catatonia, refusing to eat, refusal of treatment) and 11 patients had ECT because of treatment resistance. Mean number of ECT sessions were 7.14 ± 2.03 (minimum 5, maximum 10). All patients were on psychotropic medications. All patients were taking two ($n = 10$) or more ($n = 13$) medications. Medications included antidepressants, antipsychotics, benzodiazepines, mood stabilizers and biperiden. During the study enrollment, mean score of the HDRS was 35.70 ± 12.10 and BPRS was 30.96 ± 10.68 and after the treatment mean HRDS score was 11.32 ± 8.59 and mean BPRS score was 8.91 ± 7.11 in the patient group.

Table 1. Clinical and sociodemographic characteristics of the participants

	Depression (n=23)	HC (n=21)	F/t/ X ²	P
Age	43.04±11.69	35.43±9.34	2.37	0.022
Gender (female, %)	11 (%47.8)	11 (%52.4)	0.09	0.763
Duration of Education*	7.09±3.09	12.90±5.31	-4.49	<0.001
Marital Status (married)	16 (%69.6)	7 (%33.3)	5.78	0.016
Diagnosis ¹ (BD / MDD)	7 %30.4 / 16 %69.6			
Duration of the disorder*	12.46±11.29			
Number of hospitalizations	3.17±3.19			
Number of ECT sessions	7.14±2.03			
ECT indication (emergency / treatment resistance)	12 (%52.2) / 11 (%47.8)			
Psychiatric disorder in first degree relatives (n, %)	8 (%34.8)			
Duration of hospitalization [‡]	27.50±9.10			
CGI-before	5.87±0.82	1.00±0.00	27.36	<0.001
HDRS-before	35.70±12.10	0.81±1.57	13.10	<0.001
BPRS-before	30.96±10.68	1.86±2.73	12.12	<0.001
CGI-after	1.74±0.62			
HDRS-after	11.32±8.59			
BPRS-after	8.91±7.11			

¹Bipolar disorder depressive episode or major depressive disorder, * Years, [‡]Days, HC: Healthy controls, CGI: Clinical Global Impression, HDRS: Hamilton Depression Rating Scale, BPRS: Brief Psychiatric Rating Scale, BD: Bipolar Disorder, MDD: Major Depressive Disorder, t test or Chi-Square Test were performed.

Comparison of thiol and disulphide levels between DD and HCs are presented in Table 2. According to the Shapiro Wilks Test results, total ($p = 0.264$) and native ($p = 0.186$) thiol levels rejected the null hypothesis that the compounds were normally distributed. Disulphide ($p = 0.039$) and IMA ($p = 0.034$) levels were normally distributed. Serum total thiol levels were significantly lower in DD patients in comparison with HCs ($p = 0.032$). Difference between the groups in native thiol levels were at trend level ($p = 0.056$). Disulphide levels and disulphide to thiol levels or native to total thiol levels did not differ between the groups.

Table 2. Comparison of biochemical measures between the groups

	Depression (n=23)	HC (=21)	Z/t	p
NT*	276.95 (222.65-319.33) 273.38±58.91	306.60 (274.55-347.60) 304.94±53.29	-1.91	0.056
TT*	290.30 (243.88-328.85) 298.27±57.10	333.50 (297.75-360.10) 324.66±56.99	-2.15	0.032
SS	9.94±5.64	9.85±5.73	-0.05	0.961
SS / NT	3.94±2.70	3.24±1.84	-0.98	0.334
SS / TT	3.54±2.21	2.99±1.58	-0.94	0.355
NT / TT	92.91±4.41	94.01±3.16	0.94	0.355
Albumin	3.52±0.19	3.62±0.42	-0.99	0.327
IMA	0.62±0.14	0.32±0.26	-4.65	<0.001
IMA/Albumin	0.17±0.04	0.09±0.07	4.04	<0.001

NT: Native Thiol, TT: Total Thiol, SS: Disulphide, IMA: Ischemia Modified Albumin. HC: Healthy controls. *Mann Whitney U Test, for the analysis of other variables t test was picked.

Comparisons within the DD patients' samples before ECT, after first session and after last session are presented in Table 3. No significant difference was observed between the time points.

Table 3. Comparison of the biochemical measures within the depression group

	Before ECT	After First Session	After Last Session	F/X ²	p
NT*	276.95 (222.65-319.33) 273.38±58.91	267.00 (251.50-308.00) 270.65±54.65	270.15 (234.00-318.88) 268.04±56.79	0.04	0.978
TT*	290.30 (243.88-328.85) 293.27±57.10	288.60 (265.60-322.35) 294.37±54.29	292.90 (257.73-352.50) 292.69±61.84	0.86	0.649
SS	9.94±5.64	11.86±11.28	12.32±8.44	0.45	0.643
SS / NT	3.94±2.70	4.90±5.63	4.68±3.03	0.34	0.710
SS / TT	3.54±2.21	4.07±4.00	4.15±2.52	0.26	0.774
NT / TT	92.91±4.41	91.85±8.01	91.69±5.05	0.26	0.773
Albumin	3.62±0.42	3.51±0.53	3.65±0.33	0.53	0.593
IMA	0.62±0.14	0.59±0.18	0.58±0.18	0.33	0.724
IMA/Albumin	0.17±0.04	0.17±0.07	0.16±0.05	0.35	0.708

Abbreviations are presented in the footnote of Table 2. *Kruskal-Wallis Test, for other variables one-way ANOVA test was selected.

Correlation analysis was performed with Spearman's Rank Correlation Test. Age, education, duration of the disease,

duration of the episode, number of previous episodes, number of hospitalizations, hemogram and routine biochemistry measures, total thiol, native thiol, disulphide and IMA levels were the biochemical parameters entered to the correlation analysis. Fasting glucose levels correlated with native ($r=-0.43$, $p=0.044$) and total ($r=-0.46$, $p=0.030$) thiol levels in the DD group. No other significant correlation was observed (Table 4).

Table 4. Correlations analysis results

		Total Thiol	Native Thiol	Disulphide	IMA
Fasting Glucose	Depression	-0.46*	-0.47*	-0.11	0.03
	HC	0.06	0.05	-0.05	0.07

*Spearman's Rank Correlation Test. * $p<0.05$, ** $p<0.01$. HC: Healthy Controls. IMA: Ischemia Modified Albumin. HDRS, BPRS, CGI, serum levels of fasting glucose, urea, creatine, aspartate amino transferase, alanine aminotransferase, sodium, potassium, chlorine, thyroid stimulating hormone, white blood cell counts, hemoglobin, hematocrit and platelet counts were also entered to the correlation analysis. Only statistically significant correlations were reported.*

DISCUSSION

In this study, total thiol levels were significantly lower in patients with DD in comparison to the healthy control group. Moreover, native thiol levels were lower in the DD group compared to the healthy control group at trend level. Disulphide levels did not differ between the groups. Lower total thiol levels without decrease of disulphide levels may be due to decrease of native thiol levels. After the ECT sessions, thiol disulphide levels did not change in the DD group. NO levels were higher in the patient group in comparison to the healthy control group. However, NO level did not differ after ECT in patients with DD.

Consistent evidence indicate that DD are characterized by oxidative stress [45] and burden of oxidants might be a possible reason of the loss of cellular and subcellular components [46, 47]. Cellular components with sulfhydryl groups (-SH), also called thiols, can easily be reduced by unengaged electrons and covert into disulphide forms (-SS). Low levels of thiols might also be due to insufficient intake, or metabolic utilization (i.e. synthesis of neuromelanin or pheomelanin) as well as increased consumption by oxidation into disulphides [13]. Depletion of thiols without any change in disulphide level may indicate dietary insufficiency or enhanced consumption by metabolic utilization, rather than transformation to disulphides. Although none of the participants had nutritional insufficiency prior to study enrollment, patients with DD typically lose their appetite and thus lose weight. However, there were no significant correlation between thiol and disulphide levels and biochemical markers in this study and none of the patients reported nutritional deficiency.

Effects of ECT on oxidative stress have been investigated by few studies. In a study with schizophrenia patients, effects of ECT on serum levels of nitric oxide, malondialdehyde, glutathione, catalase were investigated [32]. Serum

samples of patients with schizophrenia were collected before ECT, after first session and after the last session. At baseline, patients had significantly higher levels of malondialdehyde and catalase levels compared to healthy controls and malondialdehyde levels decreased significantly after the last session and level of the other compounds did not differ. It is also reported that ECT normalizes total oxidant status in major depressive disorder [34] and total oxidant status / total antioxidant status ratio (oxidative stress index) in schizophrenia [34] and mania [31]. On the other hand, successful treatment with antidepressants also decrease the levels of oxidant compounds in patients with major depressive disorder [7] and antipsychotic treatment in schizophrenia [48]. It should be identified whether the reduction of oxidants is because of the ECT or remission itself. Therefore, we have made an assessment after the first session to control the effect of a single session. Thiol-disulphide levels did not differ within the DD group during the ECT course. Similarly, it has been reported that plasma thioredoxin levels in patients with mania who were treated with ECT did not change during the ECT course [33]. Thioredoxin is one of the several thiol proteins that has active sulfhydryl sites which are capable of scavenging reactive oxygen species and thus serum thioredoxin levels are vulnerable to oxidative stress [49]. Several small compounds (amino acids, peptides, thiol proteins such as thioredoxin) contribute to the thiol pool, however they are not in equilibrium and each compound may present specific oxidized/reduced ratio. Thioredoxin is a class of redox proteins facilitating the reduction of other proteins by cysteine thiol-disulphide exchange.

Levels of IMA were higher in patients with DD in comparison with the healthy control group in this study. IMA levels were not significantly enhanced in remitted patients with recurrent depressive disorder in a previous study [22]. Participants of this study were severely depressed and chemical burden might be greater during episodes in DD. Furthermore, the authors also reported that IMA levels were associated with total oxidant status in depressed patients in the study. Oxidative stress [45] neuroendocrine [29] and inflammatory changes [2, 25] are robust in DD, particularly during episodes. Moreover, IMA levels did not significantly change during the ECT course and did not show any association with disease severity in this study. The results suggest that ECT does not modify albumin molecules, which means that ECT does not produce a chemical or physical stress. Furthermore, decrease of IMA levels may require longer period for synthesis of new albumin molecules.

This study has several limitations. First, age, gender, nicotine, dietary factors, personal life style, metabolic factors may also influence the results as well as disease states in psychiatric disorders [45, 48, 50]. Furthermore, diagnoses, medications and disease stages may also have altered the results [51]. However, due to small sample size, we could not be able to analyze potential effects of the abovementioned confounders. Second, serum assessments of venous blood samples may not be fully associated with

the brain. Third, depressed patients with both major depressive disorder and bipolar disorder were enrolled into this study. Fourth, ECT parameters of the patients were personalized and thus were not standard. Fifth, albumin has several sites for drug binding and measurement of the IMA levels could be interfered in by the patients' medications. Finally, small study groups may have inflated the risk for type II statistical error. These limitations interfere with generalizability of the results and further studies are needed to confirm the results.

In summary, thiol disulphide homeostasis is assessed in patients with DD in this study. Thiols were significantly lower in the DD group, however ECT did not seem to influence thiol-disulphide levels in this study. ECT is a safe treatment modality [52-54] and these findings may provide biochemical support for the safety of ECT at subcellular level. Further controlled longitudinal studies with larger sample sizes may investigate the thiol-disulphide homeostasis in patients with DD. The effects of electrical stimulation and convulsion on redox status, chemical reactions, balance between oxidant compounds and antioxidant systems might be investigated with preclinical laboratory methods in future studies.

REFERENCES

- [1] G.B.D. Disease Injury IP, Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; 388(10053); 1545-1602.
- [2] Duval F, Mokrani, M C, Ortiz JA, Schulz P, Champeval C, Macher JP. Neuroendocrine predictors of the evolution of depression. *Dialogues Clin Neurosci*. 2005; 7(3); 273-282.
- [3] Tunc S, Atagün Mİ, Basbug HS, Erel O. Serum ceruloplasmin-ferroxidase activity in bipolar disorder is elevated compared to major depressive disorder and schizophrenia: a controlled study. *Psychiatry and Clinical Psychopharmacology*. 2019; 29(3); 307-314.
- [4] Kempton MJ, Salvador Z, Munafo MR, Geddes J, Simmons A, Simmons A, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry*. 2011; 68(7); 675-690.
- [5] Rajkowska G, Halaris A, Selemon LD. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. *Biol Psychiatry*. 2001; 49(9); 741-752.
- [6] Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP, et al. Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex*. 2002; 12(4); 386-394.
- [7] Cumurcu BE, Ozyurt H, Etikan I, Demir S, Karlidag R. Total antioxidant capacity and total oxidant status in patients with major depression: impact of antidepressant treatment. *Psychiatry Clin Neurosci*. 2009; 63(5); 639-645.
- [8] Michel TM, Frangou S, Thiemeyer D, Camara S, Jecel J, Nara K, et al. Evidence for oxidative stress in the frontal cortex in patients with recurrent depressive disorder—a postmortem study. *Psychiatry Res*. 2007; 151(1-2); 145-150.
- [9] Michel TM, Camara S, Tatschner T, Frangou S, Sheldrick AJ, Riederer P, et al. Increased xanthine oxidase in the thalamus and putamen in depression. *World J Biol Psychiatry*. 2010; 11(2 Pt 2); 314-320.
- [10] Halliwell B, Gutteridge JM. Lipid peroxidation, oxygen radicals, cell damage, and antioxidant therapy. *Lancet*. 1984; 1(8391); 1396-1397.
- [11] Jensen KS, Hansen RE, Winther JR. Kinetic and thermodynamic aspects of cellular thiol-disulfide redox regulation. *Antioxid Redox Signal*. 2009; 11(5); 1047-1058.
- [12] Turell L, Radi R, Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. *Free Radic Biol Med*. 2013; 65; 244-253.
- [13] Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. *Clin Biochem*. 2014; 47(18); 326-332.
- [14] Unal K, Erzin G, Yuksel RN, Alisik M, Erel O. Thiol/disulphide homeostasis in schizophrenia patients with positive symptoms. *Nord J Psychiatry*. 2018; 72(4); 281-284.
- [15] Cingi Yirun M, Unal K, Yirun O, Kilic OHT, Erel O. Thiol/disulphide homeostasis in manic episode and remission phases of bipolar disorder. *Nord J Psychiatry*. 2018; 72(8); 572-577.
- [16] Gumusyayla S, Vural G, Bektas H, Deniz O, Neselioglu S, Erel O. A novel oxidative stress marker in patients with Alzheimer's disease: dynamic thiol-disulphide homeostasis. *Acta Neuropsychiatr*. 2016; 28(6); 315-320.
- [17] Kabadayi Sahin E, Caykoylu A, Senat A, Erel O. A comprehensive study of oxidative stress in patients with somatic symptom disorder. *Acta Neuropsychiatr*. 2018; 1-6.
- [18] Baykan H, Durmaz, O, Baykan Ö, Alisik M, Can M, Karlidere T, et al. Dynamic thiol/disulphide homeostasis as a novel oxidative stress marker in women with major depressive disorder. *Anatolian Journal of Psychiatry*. 2018; 19(2); 135-142.
- [19] Quinlan GJ, Martin GS, Evans TW. Albumin: biochemical properties and therapeutic potential. *Hepatology*. 2005; 41(6); 1211-1219.
- [20] Marx G, Chevion M. Site-specific modification of albumin by free radicals. Reaction with copper(II) and ascorbate. *Biochem J*. 1986; 236(2); 397-400.
- [21] Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia—a preliminary report. *J Emerg Med*. 2000; 19(4); 311-315.
- [22] Tunc S, Atagun Mİ, Neselioglu S, Bilgin YY, Başbuğ HS, Erel O. Ischemia-modified albumin: a unique marker of global metabolic risk in schizophrenia and mood disorders. *Psychiatry and Clinical Psychopharmacology*. 2019; 29(2); 123-129.

- [23] Köse S, Çetin M. Ketamine and electroconvulsive therapy pairing in depression and mood disorders. *Psychiatry and Clinical Psychopharmacology*. 2017; 27(2); 103-105.
- [24] Baldinger P, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R. Neurotransmitters and electroconvulsive therapy. *J ECT*. 2014; 30(2); 116-121.
- [25] Guloksuz S, Rutten BP, Arts B, van Os J, Kenis G. The immune system and electroconvulsive therapy for depression. *J ECT*. 2014; 30(2); 132-137.
- [26] Guloksuz S, Arts B, Walter S, Drukker M, Rodriguez L, Myint AM, et al. The impact of electroconvulsive therapy on the tryptophan-kynurenine metabolic pathway. *Brain Behav Immun*. 2015; 48; 48-52.
- [27] Yrondi A, Sporer M, Peran P, Schmitt L, Arbus C, Sauvaget A. Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. *Brain Stimul*. 2018; 11(1); 29-51.
- [28] Kartalci S, Karabulut AB, Erbay LG, Acar C. Effects of Electroconvulsive Therapy on Some Inflammatory Factors in Patients With Treatment-Resistant Schizophrenia. *J ECT*. 2016; 32(3); 174-179.
- [29] Haskett RF. Electroconvulsive therapy's mechanism of action: neuroendocrine hypotheses. *J ECT*. 2014; 30(2); 107-110.
- [30] Mindt S, Neumaier M, Hellweg R, Sartorius A, Kranaster L. Brain-Derived Neurotrophic Factor in the Cerebrospinal Fluid Increases During Electroconvulsive Therapy in Patients With Depression: A Preliminary Report. *J ECT*. 2020. doi: 10.1097/YCT.000.000.0000000667. Online ahead of print.
- [31] Kalelioglu T, Genc A, Karamustafalioglu N, Tasdemir A, Gungor FC, Cansiz A, et al. Initial and post-treatment total oxidant-antioxidant status and oxidative stress index in male patients with manic episode. *Psychiatry Res*. 2014; 218(1-2); 249-251.
- [32] Kartalci S, Karabulut AB, Ozcan AC, Porgali E, Unal S. Acute and chronic effects of electroconvulsive treatment on oxidative parameters in schizophrenia patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011; 35(7); 1689-1694.
- [33] Genc A, Kalelioglu T, Karamustafalioglu N, Tasdemir A, Gungor FC, Genc ES, et al. Level of plasma thioredoxin in male patients with manic episode at initial and post-electroconvulsive or antipsychotic treatment. *Psychiatry Clin Neurosci*. 2015; 69(6); 344-350.
- [34] Senyurt M, Aybek H, Herken H, Kaptanoglu B, Korkmaz A. Evaluation of Oxidative Status in Patients Treated with Electroconvulsive Therapy. *Clin Psychopharmacol Neurosci*. 2017; 15(1); 40-46.
- [35] Durmaz O, Ispir E, Baykan H, Alisik M, Erel O. The Impact of Repetitive Transcranial Magnetic Stimulation on Oxidative Stress in Subjects With Medication-Resistant Depression. *J ECT*. 2018; 34(2); 127-131.
- [36] First MB, Spitzer RL, Gibbon M, Williams JBV. *Structured clinical interview for DSM-IV axis I disorders, clinician version (SCID-I)*. 1996, Washington, DC: American Psychiatric Press.
- [37] Ozkurkcuoglu A, Aydemir O, Yildiz M, Esen-Danaci A, Koroglu E. DSM-IV eksen I bozuklukları için yapılandırılmış klinik görüşmenin Türkçe'ye uyarlanması ve güvenilirlik çalışması. *İlac ve Tedavi Dergisi*. 1999; 12(4); 233-236.
- [38] Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23; 56-62.
- [39] Akdemir A, Turkcapar H, Orsel SD, Demirergi N, Dag İ, Ozbay H. Reliability and validity of of the Turkish version of the Hamilton Depression Rating Scale. *Compr Psychiatry*. 2001; 42:161-165.
- [40] Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962; 10; 789-812.
- [41] Andersen J, Larsen JK, Kørner A, Nielsen BM, Schultz W, Behnke K, et al. The Brief Psychiatric Rating Scale: Schizophrenia, Reliability and Validity Studies. *Nord J Psychiatry*. 1986;40:135-138,
- [42] Canbek O, Ipekcioglu D, Menges OO, Atagun MI, Karamustafalioglu N, Cetinkaya O, et al. Comparison of Propofol, Etomidate, and Thiopental in Anesthesia for Electroconvulsive Therapy: A Randomized, Double-blind Clinical Trial. *J ECT*. 2015; 31(2); 91-97.
- [43] Atay OC, Bag S, Usta H, Çetinkaya E, Yanık M. Satisfaction and attitude of bipolar patients regarding electroconvulsive therapy: modified or unmodified. *Nord J Psychiatry*. 2020; 74(2); 131-137.
- [44] Bag S, Canbek O, Atagun IM, Kutlar MT. Early effects of modern electroconvulsive therapy on subjective memory in patients with mania or depression. *Indian J Psychiatry*. 2016; 58(2); 198-203.
- [45] Michel TM, Pulschen D, Thome J. The role of oxidative stress in depressive disorders. *Curr Pharm Des*. 2012; 18(36); 5890-5899.
- [46] Ceylan D, Tuna G, Kirkali G, Tunca Z, Can G, Arat HE, et al. Oxidatively-induced DNA damage and base excision repair in euthymic patients with bipolar disorder. *DNA Repair (Amst)*. 2018; 65; 64-72.
- [47] Ravera S, Bartolucci M, Cuccarolo P, Litame E, Illarcio M, Calzia D, et al. Oxidative stress in myelin sheath: The other face of the extramitochondrial oxidative phosphorylation ability. *Free Radic Res*. 2015; 49(9); 1156-1164.
- [48] Flatow J, Buckley P, Miller BJ. Meta-analysis of oxidative stress in schizophrenia. *Biol Psychiatry*. 2013; 74(6); 400-409.
- [49] Nakamura H. Thioredoxin and its related molecules: update 2005. *Antioxid Redox Signal*. 2005; 7(5-6); 823-828.
- [50] Andreatza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, et al. Oxidative stress markers in bipolar disorder: a meta-analysis. *J Affect Disord*. 2008; 111(2-3); 135-144.
- [51] İpekçioglu D, Yazar MS, Canbek Ö, Yuksel O, Meterelliyoğ KS, İlnem MC. Electroconvulsive therapy combined with antipsychotic therapy in the treatment of acute schizophrenia inpatients: symptom profile of the clinical response. *Psychiatry and Clinical Psychopharmacology*. 2018; 28(4); 363-370.
- [52] Topping N, Sanghani SN, Petrides G, Kellner CH, Ostergaard SD. The mortality rate of electroconvulsive

- therapy: a systematic review and pooled analysis. *Acta Psychiatr Scand.* 2017; 135(5); 388-397.
- [53] Canbek O, Menges OO, Atagun MI, Kutlar MT, Kurt E. Report on 3 years' experience in electroconvulsive therapy in bakirkoy research and training hospital for psychiatric and neurological diseases: 2008-2010. *J ECT.* 2013; 29(1); 51-57.
- [54] Canbek O, Yuksel G, Atagun MI, Ipekcioglu D, Kurt E, Menges OO, et al. Geriatric ECT at a Turkish teaching hospital: a 5-year experience. *J ECT.* 2014; 30(3); e28-29.