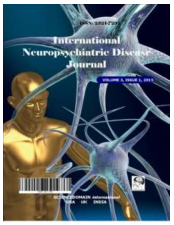

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Evidence for Oxidative Stress in Suicide Cases- A Postmortem Study

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MHK, AE and AC designed the study and wrote the protocol. Author AE collected samples. Authors MS and OO made literature search. Authors AC and USC performed the statistical analysis, and wrote the first draft of the manuscript with assistance from authors MHK, CZ and OO. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Many researchers have studied the oxidative mechanism and found that its disruption may play a role in the etiopathogenesis of certain psychiatric diseases such as major depression, bipolar disorder, attention deficit and hyperactivity disorders and schizophrenia, all of which have high suicide incidences. We aimed to investigate post-mortem suicide cases to test the hypothesis that the oxidative mechanism is disturbed by suicidal behaviours.
Methods: We performed this study on post-mortem blood samples of 35 suicide cases and 25 control patients with different mortis causa. The total antioxidant status (TAS) and total oxidant status (TOS) of the plasma were measured using a novel automated colorimetric measurement method.
Results: TAS levels were significantly higher in the suicide group compared to the control group. There was no significant difference in the TOS level between the two groups.

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Conclusion: TAS is increased in the systemic circulation of people who commit suicide. We believe that TAS and TOS may be used as a diagnostic parameter in the future after further study. Additionally, antioxidant prophylaxis may be used in psychiatric disorders to prevent suicide.

Keywords: Oxidative stress; total antioxidant status; total oxidant status; suicide; postmortem.

1. INTRODUCTION

Suicide is defined as a person intentionally ending his or her own life. Suicidal behavior is a general expression reflecting suicide and suicide attempts. The neurobiology of suicide is complex and many genetic and environmental factors to suicide have been proposed [1]. The role of heritable factors in suicidal behavior is well established, as demonstrated by postmortem brain autopsies and family studies [2]. It is claimed that genes may influence the risk for suicide through their impact on response to stress and risk of psychiatric disorder related to suicide [3].

To understand suicidal behavior, neuro-transmitters, hormones, neurochemicals and different mechanisms in organisms have been investigated to date [4]. Neurotransmitters and their receptors had been studied to understand the biology of suicidal behavior because of their roles in psychiatric impairments; levels of CSF-5HIAA were low in the suicide cases in those studies [5]. It has been reported that dysfunction of three neurobiological systems (serotonergic, dopaminergic and adrenergic) are important to the etiopathogenesis of psychiatric diseases, and the hypothalamic-pituitary-adrenal (HPA) axis has a role in suicidal behavior [6].

In neurobiological studies of suicide, how the systems play roles in the etiopathogenesis of psychiatric diseases, as mentioned above, has been investigated. The oxidative mechanism has been explored in many studies in recent years; it has been reported that in many psychiatric diseases, such as major depressive, bipolar, schizophrenia and attention deficit and hyperactivity disorders, oxidative mechanism plays a pivotal role in their etiopathogenesis [7-10]. Free radical formation is normal for an organism and may cause a breakdown of enzymes, neurotransmitters and receptor proteins [11]. They may also cause a breakdown of membrane integrity by decreasing the cell membrane permeability and fluidity [12,13]. It has been emphasized that overbalance of the oxidative mechanism may cause formation or exacerbation of psychiatric disorders by disturbing function of cell membranes, neurotransmitters and receptor proteins. Review of the literature did not produce any research studies on oxidative stress in suicide cases.

Increased risk of suicide has been reported with certain psychiatric diseases such as schizophrenia, bipolar and major depressive disorders. From these data, we aimed to investigate the oxidative mechanism in suicide attempts that resulted in death in order to test the hypothesis that the oxidative mechanism is disturbed by suicidal behaviors.

2. MATERIALS AND METHODS

Permission of the local ethics committee was obtained for the study. Included in the study were a group of cases by the manner of death ruled as suicide and a control group with other causes of death, all of which had autopsies performed prior to the study.

2.1 Blood Sampling

Venous blood samples were collected from the post-mortem samples into heparinized tubes. The blood samples were centrifuged at 3.000 rpm for 10 min at 4℃ to remove plasma. The buffy coat on the erythrocyte sediment was separated carefully. Plasma samples were stored at –80℃ until analysis.

2.2 Measurement of Variables

2.2.1 Measurement of total antioxidant status (TAS)

The total antioxidant capacity of the plasma was measured using a novel full-automatic colorimetric measurement method developed by Erel [14]. In this method Fe^{2+}-o-dianisidine complex gives a Fenton type reaction with the hydrogen peroxide to form the OH radical. This potent biological radical reacts with the substrate o-dianisidine at the reducting low pH to produce the dianisyl radical colorless o-dianisidine molecule at the reducting low pH, which is yellow-brown in color. With addition of a plasma sample, the antioxidants in the sample suppress

these oxidation reactions and inhibit color formation. This reaction is measured spectrophotometrically. The assay results are expressed as mmol Trolox Eqv./L.

2.2.2 Measurement of total oxidant status (TOS)

The total oxidative status of the plasma was measured using a full-automatic colorimetric method [15]. The oxidants in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules which is present in the the reaction medium. Ferric ions form a colored compound with xylenol orange in the acidic media. The color intensity is associated with the amount of oxidants in the sample and is measured spectrophotometrically. The results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eqv./L).

2.3 Statistical Analysis

The data were evaluated by SPSS 15.0 packaged software. The Kolmogorov-Smirnov test was used to evaluate the continuous variables in terms of normal distribution. We also used the chi-square test to evaluate nominal variables and the Mann-Whitney U test to look for continuous variables in groups, with $P<0.05$ considered statistically significant.

3. RESULTS

We performed this study on post-mortem blood samples of 35 suicide cases and 25 control patients with different mortis causas. TAS levels were found significantly higher in the suicide group compared to controls (Table 1). There was no significant difference in TOS level between the groups. Age, gender, TAS and TOS levels of groups are shown in Table 2.

Table 1. Test statistics[a]

	TAS	TOS
Mann-Whitney U	1224,000	701,000
Wilcoxon W	3054,000	2531,000
Z	-2,519	-5,409
Asymp. sig. (2-tailed)	,012	,000

a. Grouping variable: Groups

4. DISCUSSION

The Glutathion levels of post-mortem bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCH) patients' prefrontal cortex tissues were found to be lower. It was reported that these patient groups were more sensitive to oxidative stress. This study shows that oxidative stress, known to occur in psychiatric patients, can be present post-mortem [16]. There was no significant difference between suicidal patients and the control group in terms of TAS and TOS in our study. We could not compare our results to other studies of post-mortem TAS levels, TOS levels or oxidative stress because ours was the first.

However, we did find significantly higher levels of nitric oxide metabolites (NOX) and lipid hydroperoxides and lower total radical-trapping anti-oxidant parameter (TRAP) in depressive patients who had attempted suicide versus those who had not. Vargas et al. found increased oxidant levels and decreased antioxidant levels in individuals with history of suicide attempt and they concluded that increased oxidant levels as well as lowered antioxidant levels could play a role in the pathophysiology of suicidal behavior independently from the effects of depression [1]. In a study of plasma, NOX was higher in depressive patients who had attempted suicide versus depressive patients who had not (control group) [17]. In that study, it was found that high levels of plasma NOX correlated with the lethality of the suicide attempts.

Table 2. Age, gender, TAS and TOS levels of groups

	Suicide (n:35)	Control (n:25)	p
Age (mean±sd)	31.63±15.93	40.04±19.38	>0.05
Gender			>0.05
Male (%)	40 (71.4%)	19 (76.0%)	
Female (%)	16 (28.6%)	6 (24.0%)	
TAS (mmol Trolox Eqv./L) (median, min-max)	1.99, 0.5-4.08	1.40, 0.07-3.45	0.027
TOS (μmol H_2O_2 Eqv./L) (median, min-max)	24.32, 0.12-5623.0	17.46, 0.93-158.02	>0.05

TAS: Total antioxidant status, TOS: Total oxidant status, sd: Standard deviation

Table 3. Possible reasons of suicide cases

Histories of suicide cases	n	%
Depression	4	11.4
Schizophrenia	1	2.9
Prostate cancer	1	2.9
Unknown psychiatric disorder (using unknown psychiatric medications)	3	8.6
Homicide	3	8.6
Economic problems	7	20
No information	7	20
No medical or pscyhiatric condition	9	25.7
Total	35	100

Many parameters of oxidative metabolism have been studied in major psychiatric diseases, such as MDD, SCH and BD, which increase suicide risk. In a review, oxidative metabolism was indicated in major depression with a low level of antioxidants. In contrast, other studies indicated an increase in antioxidants [9]. Although it has been reported that the antioxidant level was low in the studies that investigated oxidative metabolism in patients with schizophrenia, it has been shown that the antioxidant level did not change or increased [18-23]. There are also studies that have confirmed that TAS and other antioxidant levels are increased in patients with bipolar disorder [24,25]. In psychiatric diseases that increase suicide risk, such as MDD, SCH and BD, the oxidative mechanism has deteriorated, and while it has generally been shown that oxidants are increased and antioxidants are decreased, there are opposite evidence, hence the results are contradictory.

We hypothesized that we would find increased antioxidants and decreased oxidants in suicide cases, but we found that oxidant capacity does not change, and antioxidant capacity increased in suicide cases, so our findings didn't affirm our hypothesis. This increased antioxidant capacity can be thought of as a compensatory mechanism, which may cause suicidal tendencies by damaging the brain like an autoimmune response.

In a limited number of studies, as mentioned above, the interaction of suicide with oxidative stress was researched; increased levels of SOD, an antioxidant enzyme, and NO, an oxidant molecule, were seen in the suicide cases. Although our study revealed differences between suicide and control cases in terms of oxidative stress, more study is needed on this issue.

There are several limitations of our study. Firstly, sample size is small. Second, our study can be questioned because it lacked data about some of the medical histories of participants, e.g., alcohol, smoking, comorbidity, usage of antioxidants and drug addiction as well as how soon autopsies were performed. In the present study, four cases had depression, one case was prostate cancer, seven cases had money problems. Three cases were having psychiatric treatment (diagnoses' were unknown), three cases had committed homicide and history of medical records of seven cases were unknown. Many of these cases could be in depression. As it is known that oxidative stress is elevated in major depression, our findings could be effected from this psychiatric disorder. So one must be cautious when interpreting these results. Neverthless, the association between suicide and psychiatric disorders is not linear [26], and in our study 25.7% of the cases (n=9) had neither psychiatric symptoms nor psychiatric treatment history in their medical records.

5. CONCLUSION

In conclusion, these results show that there is a positive association between increased total antioxidant levels and suicidal behavior. Many factors contribute to the development of suicidal behavior and not all of these factors are known. Therefore, our results can only depict associations and not causality. This is the first study to investigate and compare oxidative stress of suicide victims and those of different mortis causa. It can also lead the way for new studies about oxidative stress and suicide.

CONSENT

Permission of Morgue Department of the Adana Branch of the Council of Forensic Medicine was obtained for the study. Informed consent was not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vargas HO, Nunes SOV, de Castro MP, et al. Oxidative stress and lowered total antioxidant status are associated with a history of suicide attempts. J Affect Disord. 2013;150:923-30.
2. Currier D, Mann JJ. Stress, genes and the biology of suicidal behavior. Psychiatr Clin North Am. 2008;31:247-69.
3. Kendler KS. Genetic and environmental pathways to suicidal behavior: Reflections of a genetic epidemiologist. Eur Psychiatry. 2010;25:300-3.
4. Ernst C, Mechawar N Turecki G. Suicide neurobiology. Prog Neurobiol. 2009;89: 315-33.
5. Mann JJ. The neurobiology of suicide. Nat Med. 1998;4:25-30.
6. Van Heeringen K. The neurobiology of suicide and suicidality. Can J Psychiatry. 2003;48:292-300.
7. Andreazza 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;111:135-44.
8. Bošković M, Vovk T, Plesničar BK, Grabnar I. Oxidative stress in schizophrenia. Curr Neuropharmacol. 2011;9:301.
9. Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry. 2011;35:676-92.
10. Selek S, Bulut M, Ocak AR, Kalenderoğlu A Savaş HA. Evaluation of total oxidative status in adult attention deficit hyperactivity disorder and its diagnostic implications. J Psychiatr Res. 2012;46:451-5.
11. Repine JE, Bast A, Lankhorst IDA. Oxidative stress in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;156:341-57.
12. Ball SS, Weindruch R, Walford RL. Antioxidants and the immune response. Free Radicals, Aging and Degenerative Diseases 2nd ed. New York: Alan R. Liss Inc; 1986.
13. Braughler JM, Chase RL Pregenzer JF. Oxidation of ferrous iron during peroxidation of lipid substrates. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism. 1987;921:457-64.
14. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem. 2004;37:112-9.
15. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem. 2005;38:1103-11.
16. Schlicht K, Büttner A, Siedler F, Scheffer B, Zill P, Eisenmenger W, et al. Comparative proteomic analysis with postmortem prefrontal cortex tissues of suicide victims versus controls. J Psychiatr Res. 2007;41:493-501.
17. Kim YK, Paik JW, Lee SW, Yoon D, Han C, Lee BH. Increased plasma nitric oxide level associated with suicide attempt in depressive patients. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1091-6.
18. Ben Othmen L, Mechri A, Fendri C, Bost M, Chazot G, Gaha L, et al. Altered antioxidant defense system in clinically stable patients with schizophrenia and their unaffected siblings. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:155-9.
19. Dadheech G, Mishra S, Gautam S, Sharma P. Evaluation of antioxidant deficit in schizophrenia. Indian J Psychiatry. 2008;50:16-20.
20. Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog

Neuropsychopharmacol Biol Psychiatry. 2008;32:1677-81.
21. Matsuzawa D, Obata T, Shirayama Y, Nonaka H, Kanazawa Y, Yoshitome E, et al. Negative correlation between brain glutathione level and negative symptoms in schizophrenia: A 3T 1H-MRS study. PLoS One. 2008;3:e1944.
22. Reddy R, Keshavan M, Yao JK. Reduced plasma antioxidants in first-episode patients with schizophrenia. Schizophr Res. 2003;62:205-12.
23. Yao JK, Reddy RD van Kammen DP. Human plasma glutathione peroxidase and symptom severity in schizophrenia. Biol Psychiatry. 1999;45:1512-5.
24. Kuloglu M, Ustundag B, Atmaca M, Canatan H, Tezcan AE, Cinkilinc N. Lipid peroxidation and antioxidant enzyme levels in patients with schizophrenia and bipolar disorder. Cell Biochem Funct. 2002;20: 171-5.
25. Yumru M, Savas HA, Kalenderoglu A, Bulut M, Celik H, Erel O. Oxidative imbalance in bipolar disorder subtypes: a comperative study. Prog Neuro-psychopharmacol Biol Psychiatry. 2009; 33:1070-4.
26. Mandelli L, Carli V, Serretti A, Sarchiapone M. Suicidal behavior: Genes, environmental stress and temperamental traits. Suicidologi. 2015;16:2.

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