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Research Paper: The Role of Oxidant-Antioxidant Status in Suicide Behavior in Kurdish Ethnicity

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ABSTRACT

Introduction: Oxidative stress plays a critical role in the pathogenesis of neurodegenerative and neuropsychiatric disorders. However, its role in suicidal behavior has not been clarified yet. Consequently, we aimed to evaluate the oxidant-antioxidant status in the serum of suicide attempters in Ilam city.

Methods: Fifty suicide attempters and 40 control subjects (volunteers) aged 18-35 years were studied in the current experiment. To consider the oxidant-antioxidant status, serum levels of Malondialdehyde (MDA), Nitric Oxide (NO), Superoxide Dismutase (SOD), and the Total Antioxidant Capacity (TAC) were measured.

Results: Serum levels of SOD and TAC were significantly lower in the suicide attempters group compared to the controls. Furthermore, serum NO level was significantly higher in the suicide attempters compared to the control groups. Interestingly, the serum level of MDA was significantly lower in the suicide attempters compared to the control groups.

Conclusion: The oxidative stress without MDA elevation, detected in suicide attempters, can be considered a biochemical hallmark in suicide behavior.

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Highlights

- Oxidative and nitrosative stress may play role in the pathogenosis of suicidal behavior.
- MDA level decreases in people with risk of suicide.
- Oxidative stress occurs when there is an imbalance between free radical generation and antioxidant capacity

Plain Language Summary

Suicide is a complex behavior and different factors, including environmental factors, social facilities, health and supportive systems. Increasing antioxidant content of daily diet may be used as a strategy to decrease suicidal behavior in high risk people. Oxidative stress occurs when there is an imbalance between free radical generation and antioxidant capacity. Oxidative stress plays a role in the aging and pathogenesis of neurodegenerative diseases, like Alzheimer's disease, Huntington's disease, and Parkinson's disease. This study aimed to investigate the correlation between oxidant-antioxidant levels and suicidal behavior.

1. Introduction

Suicide is a world health priority and the second leading cause of death in people aged 15-29 years old. According to the World Health Organization (WHO), about 10.7 per 100,000 people die from suicide every year (Bertolote & Fleischmann, 2015). According to a study by Kiadaliri et al., attempted suicide have increased to 16.3 per 100,000 population in 2003 in Iran (Kiadaliri, Saadat, Shahnavazi, & Haghparast-Bidgoli, 2014); however; Ilam province has the highest rate of suicide in the country; 19.53 per 100,000 people in the last 10 years, which is much higher than the global statistics (Bertolote & Fleischmann, 2015; Kiadaliri, Saadat, Shahnavazi, & Haghparast-Bidgoli, 2014). Suicide is a complex behavior and different factors, including environmental factors, social facilities, health and supportive systems, relationships, demographic characteristics, and biological factors can play a role in suicidal behavior (Banerjee, Ghosh, Ghosh, Bhattacharyya, & Mondal, 2013; Ernst, Mechawar, & Turecki, 2009; Fu et al., 2002). Oxidative stress, neurotransmitters imbalance, mitochondrial dysfunction, etc. as biological factors are some key findings in the pathogenesis of Central Nervous System (CNS)-related diseases (Bagheri, Rezakhani, Roghani, Joghataei, & Mohseni, 2015; Huang et al., 2019; Reddy, 2017).

Mainly, oxidative stress occurs when there is an imbalance between free radical generation and antioxidant capacity (Salim, 2017). The brain is highly susceptible to oxidative stress due to the high consumption of oxygen, high content of unsaturated fatty acids, high content of Lipid Peroxidation (LP), and weak antioxidant systems (Finkel & Holbrook, 2000). Oxidative stress plays a role in the aging and pathogenesis of neurodegenerative diseases, like Alzheimer's disease, Huntington's disease, and Parkinson's disease (Bagheri, Joghataei, Mohseni, & Roghani, 2011; Ghofrani et al., 2015; Salim, 2017). In addition, recent studies have highlighted the role of oxidative stress in the pathogenesis of neuropsychiatric disorders, as a high level of lipid peroxidation in Schizophrenia (SZ) and Bipolar Disorder (BD) has been reported by Kunz et al. (2008); Nunomura, Tamaoki, & Motohashi, (2014); Steenkamp et al., (2017). Furthermore, a strong correlation between oxidative stress and anxiety symptoms has been found in patients with Major Depressive Disorder (MDD) (Steenkamp et al., 2017). However, the upshot of oxidative stress in suicide attempters has not yet been inspected.

On the other hand, interviews and questionnaires have been widely used by psychiatrists to identify people with different psychiatric disorders or suicide risk, while in many cases, the diagnostic process is failed. Consequently, we aimed to investigate the correlation between oxidant-antioxidant levels and suicidal behavior in Kurdish ethnicity in Ilam province.

2. Methods

Two different groups were evaluated in the present experiment; group one: hospitalized suicide attempters (n=50) who were admitted to the emergency room of Mostafa Khomeini hospital in Ilam during spring and autumn 2018 and group two: healthy control subjects without a history of suicide (n=40). Notably, 239 individuals were included in the experiment in phase one,

but some were excluded due to inclusion and exclusion criteria, which are noted in Table 1.

All individuals in groups one and two were matched by sex and age (18-35 years old) and were interviewed by a trained nurse using a prepared structural questioner for demographic information and psychiatric and medical histories that are summarized in Table 1. They were all medication-free for at least eight weeks. The subjects in group one were evaluated for Major Depressive Disorder (MDD) using the Beck Depression Inventory (BDI-II), and those without MDD were selected for the experiment. The exact cause of suicide is usually a mystery, but attempters using physical means, gun shut, and self-burning were not included in the study since they are admitted to another center.

The study protocol was approved by the Ethics Committee of Ilam University of Medical Sciences (Code: IR.MEDILAM.REC.1397.057). After a complete description of the study for subjects, written informed consent was obtained from each of them.

Sample collection

Approximately 10 ml of blood samples were collected from all individuals (groups one and two) from 8:30-10:30 am. In group one, samples were taken following an overnight admission.

Afterward, the whole blood was collected in a non-coagulant tube, and it was allowed to clot at room temperature for around 30 min and centrifuged at 1000xg for 15 min. The supernatant was aspirated carefully as serum and stored at -80° C until use.

Measurement of total antioxidant capacity

Ferric Ion Reducing Antioxidant Power (FRAP) Assay was used to measure total antioxidant capacity (NaxiferTM Kit). FRAP activity was measured according to the method of Benzie and Strain (Benzie & Strain, 1996). Briefly, acetate buffer (300 mM, pH 3.6), TPTZ (2,4,6-tripyridyls-triazine) 10 mM in 40 mM HCl, and FeCl3·6H2O (20 mM) were mixed at the ratio of 10: 1: 1 to obtain the FRAP reagent. Also, 5 µL of the samples were mixed with 250 µL of FRAP reagent, and absorbance was measured at 593 nm after vortexing.

Measurement of lipid peroxidation

Lipid peroxidation was evaluated by measuring the amount of MDA in serum samples using Nalondi Kit ™. Briefly, 100 µl serum was diluted with 500 µl with distilled water and kept in a boiling water bath for 15 min. Then, 1 mL of trichloroacetic acid TCA-2-thiobarbituric acid (TBA)–HCl reagent was added to the diluted sample. The reaction mixture was cooled and centrifuged. The supernatant was collected and the optical density of the pink color was read at 535 nm.

Measurement of superoxide dismutase

Superoxide Dismutase (SOD) activity assay was done according to the Marklund method (Marklund & Marklund, 1974). SOD activity was measured through pyrogallol autoxidation. Pyrogallol autoxidation was inhibited in the presence of SOD and SOD activity was indirectly measured at 420 nm. A calibration curve was performed with purified SOD as a standard.

Measurement of nitric oxide

NO levels were measured according to the Griess method (Sun, Zhang, Broderick, & Fein, 2003). In this method, nitrite was first treated with sulfanilamide in acidic media to form a transient diazonium salt. Then it was allowed to react with N-naphthyl-ethylenediamine to form a stable azo compound. Finally, purple color density was measured at the absorbance of 540 nm.

Statistical analysis

The data analysis was done using Graph pad Prism 6. The differences between the groups were evaluated by the independent sample t-test. A $P<0.05$ was considered as a significant difference.

3. Results

Table 1 shows the demographic characteristics of the participants. The Mean±SD age of participants was 26.7±0.7 and 29.3±0.6 years in suicide attempters and control groups, respectively. The mean Body Mass Index (BMI) in suicide attempters was 24.7±0.5 kg/m^2, which showed no statistical difference compared to the controls (25±0.3 kg/m^2).

The Mean±SD serum levels of SOD in the control subjects and suicide attempters are shown in Figure 1. The mean serum levels of SOD were 692.6± 73.8 U/ml in the suicide attempters, which was significantly lower than the control group (934.8±79.2 U/ml; $P<0.05$).

Figure 2 shows the serum levels of TAC in the control individuals and the group with a suicide attempt. The mean serum levels of TAC in the suicide group were

Table 1. Demographic characteristics of the participants

Characteristics	Mean±SEM	
	Suicide Attempt (n=50)	Normal Control (n=40)
Age (years)	26.7±0.7	29.3±0.6
BMI (kg/m²)	24.7±0.5	25±0.3
Smoking	None	None
Alcohol abuse	None	None
Confirmed psychiatric illness	None	None
Metabolic disease	None	None
Other disease	None	None
Surgery in the last six months	None	None
Medication	None	None

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1.8±0.1 mM/L, which was significantly lower than the control group (2.2±0.1 mM/L; P<0.05).

The mean serum levels of MDA in the controls and suicide attempters are shown in Figure 3, which were 0.90±0.05 nM/ml in the suicide group and were significantly lower than the control group (1.1±0.04 nM/ml; P<0.01). Figure 4 shows the mean serum levels of NO in the controls and suicide attempters. The mean serum levels of NO in suicidal attempters was 0.07143±0.00005 µM, which was significantly higher than the control group (0.07125±0.000016 µM; P<0.01).

4. Discussion

Here, the findings showed a significant decrease in the serum levels of SOD and TAC in suicide attempters. In addition, the mean serum levels of NO were significantly higher in suicide attempters compared to the controls. Interestingly, the serum levels of MDA were significantly lower in the suicide attempters. These observations may reflect the presence of oxidative stress in the subjects with a suicide attempt.

Several factors may affect oxidant/ antioxidant balance in body fluids. Unhealthy lifestyles, such as smoking and alcohol consumption, and some diseases, like diabetes

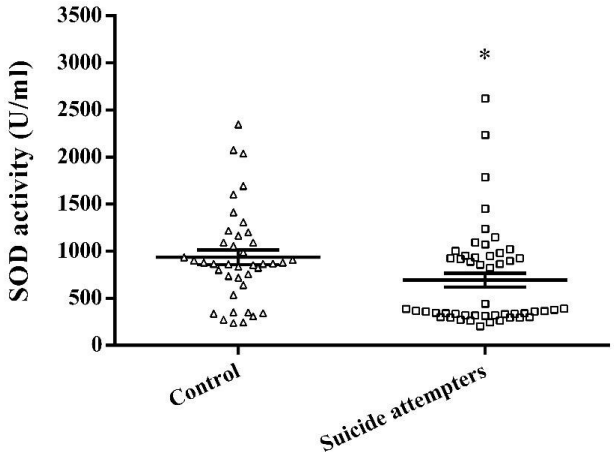

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Figure 1. Serum levels of Total Antioxidant Capacity (TAC) in the control group and suicide attempters

The graph represents Mean±SEM in the different groups; * Indicates a significant difference between the groups (P<0.05).

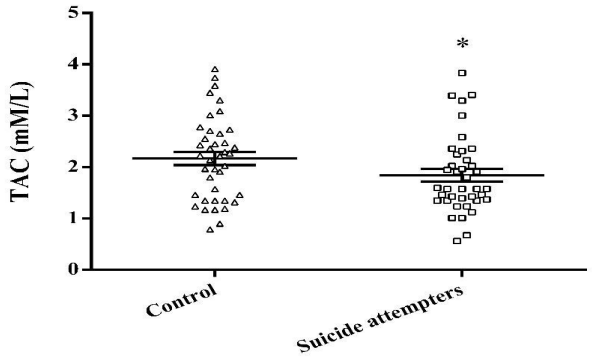

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Figure 2. Serum levels of Superoxide Dismutase (SOD) in the control group and suicide attempters

The graph represents Mean±SEM in different groups; * Indicates a significant difference between the groups (P<0.05).

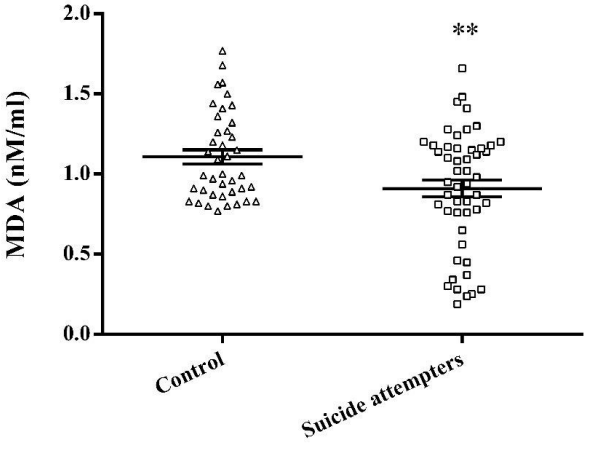

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Figure 3. Measurement of Malondialdehyde (MDA) serum concentrations in the control group and suicide attempters

The graph represents Mean±SEM in different groups; **Indicates a significant difference between the groups (P<0.01).

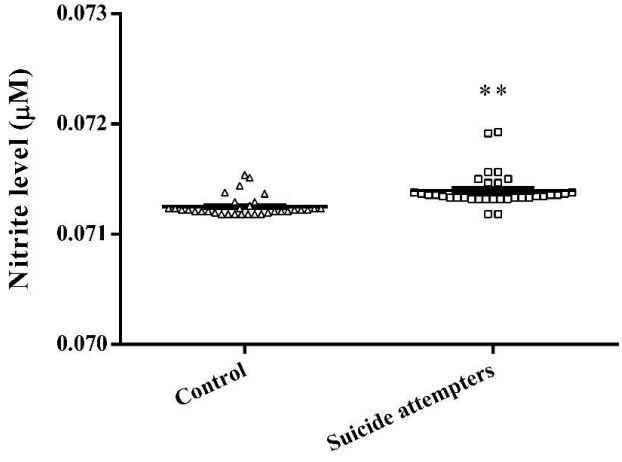

Figure 4. Serum levels of Nitric Oxide (NO) in the control group and suicide attempters

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The graph represents Mean±SEM in different groups; **Indicates a significant difference between the groups (P<0.01).

can increase Reactive Oxygen Species (ROS) production and induce oxidative stress (Newsholme, Cruzat, Keane, Carlessi, & de Bittencourt, 2016; PopaWagner et al., 2020). Consequently, the participants with a history of smoking, alcohol consumption, and metabolic diseases were excluded from the experiment.

Diet is another factor that may alter serum oxidant/antioxidant status. A high fat diet for 16 weeks can induce oxidative stress and lead to endoplasmic reticulum stress in muscle fiber and hepatocytes (Salari et al., 2015; Yuzefovych, Musiyenko, Wilson, & Rachek, 2013). Conversely, calorie restriction reduces ROS production and prevents oxidative stress (Balaban, Nemoto, & Finkel, 2005). Since it was difficult to determine long-term calorie intake in participants, BMI was measured as an indicator of calorie intake and all subjects were in the same spectrum of BMI values.

Vitamins have the potential to modify oxidant-antioxidant balance. Vitamins A, C, and E have antioxidant activity and dietary supplement consumption has the potential to change serum antioxidant levels (Li, Li, Wu, Huang, & Jiang, 2012). However, adding β-carotene and vitamins C and E to the diet cannot alter serum antioxidant levels (Gawron-Skarbek et al., 2017). Notably, in order to remove the effect of vitamins, participants with dietary supplements consumption were excluded from the study.

The decreased levels of serum antioxidants (SOD and TAC) and increased levels of free radicals (NO) showed the presence of oxidative stress in suicide attempters. Vargas et al. (2013) reported the decreased levels of TAC and increased levels of NO in individuals with a history of suicide. However, they did not detect any changes in serum MDA levels. Here, MDA levels were significantly lower in suicide attempters compared to the control group. MDA is one of the final products of polyunsaturated fatty acids (PUFAs) peroxidation in cells (Tsikas, 2017). Recent researches have highlighted the role of PUFAs monitoring in MDD (Parekh, Smeeth, Milner, & Thure, 2017). Decreased levels of Eicosapentaenoic Acid (EPA) have been reported in the RBC membrane of suicide attempters. Furthermore, serum levels of EPA and Docosahexaenoic Acid (DHA) have been lower in US military suicide attempters in comparison with the controls (Huan et al., 2004; Lewis et al., 2011; Sublette, Hibbeln, Galfalvy, Oquendo, & Mann, 2006). Since MDA concentrations can be affected by PUFAs concentration (Tsikas, 2017; Zghibeh, Gopal, Poff, Falck, & Balazy, 2004), decreased levels of MDA may result from low serum levels of PUFAs in the suicide attempters. We concluded that the occurrence of imbalance in the oxidant/ antioxidant system is associated with suicidal behavior and supervenes along with the MDA decreased levels. These findings may highlight the way to detect the high-risk subjects and may facilitate the way to investigate the pathogenesis of suicide behavior.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the ethics committee of the Ilam University of Medical Sciences.

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Ilam University of Medical Sciences covered the financial costs of the present study.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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