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ORIGINAL PAPER

Altered lipid peroxidation markers are related to post-traumatic stress disorder (PTSD) and not trauma itself in earthquake survivors

Abdullah Atli[1] · Mahmut Bulut[1] · Yasin Bez[2] · İbrahim Kaplan[3] · Pınar Güzel Özdemir[4] · Cem Uysal[5] · Hilal Selçuk[6] · Aytekin Sir[1]

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Abstract The traumatic life events, including earthquakes, war, and interpersonal conflicts, cause a cascade of psychological and biological changes known as post-traumatic stress disorder (PTSD). Malondialdehyde (MDA) is a reliable marker of lipid peroxidation, and paraoxonase is a known antioxidant enzyme. The aims of this study were to investigate the relationship between earthquake trauma, PTSD effects on oxidative stress and the levels of serum paraoxonase 1 (PON1) enzyme activity, and levels of serum MDA. The study was carried out on three groups called: the PTSD group, the traumatized with earthquake exercise group, and healthy control group, which contained 32, 31, and 38 individuals, respectively. Serum MDA levels and PON1 enzyme activities from all participants were measured, and the results were compared across all groups. There were no significant differences between the PTSD patients and non-PTSD earthquake survivors in terms of the study variables. The mean PON1 enzyme activity from PTSD patients was significantly lower, while the mean MDA level was significantly higher than that of the healthy control group ($p < 0.01$ for both measurements). Similarly, earthquake survivors who did not develop PTSD showed higher MDA levels and lower PON1 activity when compared to healthy controls. However, the differences between these groups did not reach a statistically significant level. Increased MDA level and decreased PON1 activity measured in PTSD patients after earthquake and may suggest increased oxidative stress in these patients. The nonsignificant trends that are observed in lipid peroxidation markers of earthquake survivors may indicate higher impact of PTSD development on these markers than trauma itself. For example, PTSD diagnosis seems to add to the effect of trauma on serum MDA levels and PON1 enzyme activity. Thus, serum MDA levels and PON1 enzyme activity may serve as biochemical markers of PTSD diagnosis.

Keywords PTSD · Earthquake · Lipid peroxidation · Biological markers · Oxidative stress

✉ Abdullah Atli
abdullahatli@yandex.com

[1] Department of Psychiatry, Dicle University, 21280 Diyarbakir, Turkey

[2] Department of Psychiatry, Marmara University, Istanbul, Turkey

[3] Department of Biochemistry, Dicle University, Diyarbakir, Turkey

[4] Department of Psychiatry, Yuzuncu Yil University, Van, Turkey

[5] Department of Forensic Medicine, Dicle University, Diyarbakir, Turkey

[6] Department of Psychiatry, Selhaddin Eyyubi State Hospital, Diyarbakir, Turkey

Introduction

There is mounting evidence indicating that lipid peroxidation markers, including MDA and PON1, are involved in the initiation and development of many different forms of psychiatric pathologies [1]. Post-traumatic stress disorder (PTSD) is a psychiatric condition that is characterized by symptoms of hypermnesia from the traumatic event, hyperarousal, and avoidance behavior that can develop in response to a traumatic life event. PTSD was defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as an event that involves life endangerment, death, or serious injury or threat and is

accompanied by feelings of intense fear, horror, or helplessness [2].

The estimated lifetime prevalence of PTSD was reported as 7.8 % in adults with female predominance [2]. Particularly, higher rates of PTSD development among earthquake survivors have been reported, ranging between 11.2 and 43 % [3–5]. In most of the studies up to date, various metabolic and hormonal changes that are known to result in somatic symptoms have been observed in PTSD [6]. Although various biochemical factors secondary to traumatic stress have been determined to have role in the etiology of PTSD, the etiopathogenesis has not been well characterized [7].

Oxidative stress is a biological condition that accompanies mental disorders and has drawn attention in recent years [8–12]. Several studies suggested an association between oxidative stress and psychiatric disorders, including the anxiety disorders such as panic disorder [13], obsessive–compulsive disorder [14], generalized anxiety disorder [11], social phobia [15], and PTSD [16–18]. Nevertheless, results of the previous studies about PTSD seem to be inconclusive [16–18]. In those studies, the markers of oxidative stress were reported to be unrelated to PTSD in general. However, there have been reports suggesting a role for MDA, which is a marker of lipid peroxidation during oxidative mechanisms [16, 17].

MDA is a reliable marker of lipid peroxidation during the breakdown and oxidation of polyunsaturated fatty acids. PON1 is an antioxidative enzyme that protects against lipid peroxidation [19]. Although increased levels of MDA have been previously shown in adults with PTSD, the levels of PON1 have not been studied.

Attari et al. [16] found that MDA levels were higher in a case group, while peroxidant capacity was higher in the healthy control group. Tezcan et al. [17] found that MDA levels of the patients did not differ from those of the healthy controls and the MDA levels were significantly correlated with CAPS scores.

Paraoxonases (PONs) were originally discovered for their role in hydrolysis of exogenous toxic organophosphate compounds such as paraoxon and aromatic esters (such as phenyl acetate) [20]. Paraoxonase deficiency has been shown to be related to increased susceptibility to lipid peroxidation. PONs are high-density lipoprotein (HDL)-associated enzymes that protect both low-density lipoprotein (LDL) and HDL from oxidative modification [21]. The currently known family of the PONs consists of three members: PON1, PON2, and PON3, which are encoded by three separate genes on the same chromosome. PON1 attracted significant interest for its role in antioxidant properties of HDL cholesterol (HDL-C) [20]. The existence of an enzymatic mechanism is supported by the observation that heat inactivation of purified PON1 abolishes its antioxidant effect. The exact antioxidant mechanism of PON1 is not yet known. However, it is known that its protective effect does not stem from chelating of copper ions or its potential lipid transfer from LDL-C to HDL-C. Furthermore, growing evidence supports atheroprotective effects of PON1 activity [22].

The design of the previous studies has not allowed us to differentiate the effects of trauma itself and PTSD diagnosis on oxidative stress parameters. When taken together, the lipid peroxidation marker MDA and PON1 have not been throughly studied in PTSD patients. Based on these data, we aimed to investigate the level of MDA and PON1 enzyme activity in survivors of the Van 2011 earthquake and to compare them to healthy subjects never exposed to an earthquake in their lifetime.

This methodological design may enable us to understand the possible differences caused by the diagnosis itself. The results of this study and its effect on traumatic events and oxidative stress parameters will be discussed.

Materials and methods

Patients and controls

Two serious earthquakes occurred on October 23, 2011, and November 9, 2011, with the magnitudes of "7.0" and "5.6," respectively, in Van, which is located in the eastern part of Turkey. According to the report of the Prime Ministry Disaster and Emergency Management Presidency (AFAD) of Republic of Turkey, 197,903 people were placed in various temporary shelters after the earthquakes that occurred in the Van area. As a result of these earthquakes, 644 people died and 252 people were rescued from the rubble, while 1,966 people were injured [23].

Participants of all groups were informed about the nature of the study. The medical history was collected concerning sociodemographics and clinical factors also detailed in the psychiatric and diagnostic examinations that were performed by experienced authors.

This study consisted of one patient group and two control groups. These groups are: Group 1: Patients who were diagnosed with PTSD according to DSM-IV diagnostic criteria after the earthquakes; Group 2: Participants who did not develop PTSD even after exposing to the earthquakes; and Group 3: Participants who have never been exposed to any trauma and have not been diagnosed with PTSD.

Participants in the Groups 1 and 2 were selected among the Van earthquake survivors, whereas Group 3 was composed of healthy people living in Diyarbakir. This city is located in the southeastern part of Turkey which has not witnessed an earthquake for the last four decades. Thirty-two PTSD patients were involved in Group 1, thirty-two healthy controls from

Van area were involved in Group 2, and thirty-eight healthy controls from Diyarbakir area were involved in Group 3.

Exclusion criteria included: current (1) comorbid Axis I or II conditions according to DSM-IV criteria; (2) substance abuse or dependence; (3) any history of mental disabilities; (4) chronic or serious medical problems such as diabetes mellitus and hypertension; (5) pregnancy; (6) neurological disorders like epilepsy; (7) use of any vitamin or fish oil; (8) severe head injury; and (9) blood stored in inappropriate conditions, such as hemolyzed, not stored in a refrigerator, not centrifuged, or insufficient amount of blood. Patients that did not consent to participate in the study were also excluded.

The study protocol was approved by the Dicle University Regional Research Ethics Committee, prior to initiation of this study, and was conducted in compliance with the revised version of the Helsinki Declaration and the principles set forth by the Ministry of Health of the Turkish Republic for clinical studies. All participants gave written informed consent for the study.

Clinical measurements

Diagnosis of patients was made according to a trained psychiatrist and the DSM-IV criteria using the Structured Clinical Interview for DSM-IV. Also, a semi-structured form was prepared by experienced authors and was used to collect demographic and clinical variables for all participants.

PTSD Checklist-Civilian Version (PCL-C) and Clinical Global Impression-Severity of Illness (CGI-S) were administered to Group 1. PCL-C was also administered to Group 2.

Following collection from each group, the data were compared to each other in terms of the demographic and clinical characteristics such as age, gender, smoking status, BMI, history of psychiatric disorder, family history of psychiatric disorder, and biochemical measurements.

Blood sampling

A 2 ml venous blood sample was obtained for biochemical tests. After 12 h of fasting, venous blood samples from all participants were collected at 8:00 a.m. Serum samples were separated from the blood by centrifugation at 3000 rpm for 10 min and stored at −80 °C.

Lipid peroxidation markers

MDA levels and PON1 activity were measured in serum samples of the study groups. PON1 activity and MDA level measurements were performed at a single time point. The tests were performed according to the manufacturer's instructions. The optical density of each well was measured using an automated microplate reader.

(a) *Measurement of MDA level* Serum lipid peroxidation (MDA) was measured by a colorimetric thiobarbituric acid (TBA) method [24]. Lipid peroxides break down to form MDA with thiobarbituric acid (TBA) at pH 2–3 and 95 °C for 15 min. The latter compound reacts with TBA to form a pink pigment with a maximal absorption at 532 nm.

(b) *Measurement of paraoxonase 1 activity* Serum PON1 activity was measured spectrophotometrically by a modified Eckerson method. Initial rates of hydrolysis of paraoxon (0.0-diethyl-0-p-nitrophenylphosphate; Sigma Chemical Co., London, UK) were determined by measuring liberated- p-nitrophenol at 405 nm at 37 °C [25].

Statistical analysis

All statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS) for Windows 15.0. Data were presented as the mean (M) ± standard deviation (SD), for parametric variables. Chi-square test was used to compare the frequencies between groups. The normality of distribution was tested by Kolmogorov–Smirnov test. The continuous variables were compared between groups by using ANOVA, and post hoc analyses were performed accordingly. Pearson's correlation analysis was performed to evaluate the relationship between the study variables. A p value of >0.05 was accepted as statistically significant.

Results

In accordance with the aim of the present study, each group (Groups 1, 2, and 3) was analyzed. The patient group (Group 1) and the control groups (Groups 2 and 3) were evenly matched in terms of age, gender, body mass index (BMI), and smoking status (Table 1).

Education

The mean education level for each group was assessed (Group 1 = 7.3 ± 4.7 years/Group 2 = 12.5 ± 4.7 years/Group 3 = 13.2 ± 4.2 years, respectively). Education level of patients with PTSD was significantly lower than those of the other two groups (Table 1).

History of psychiatric diagnosis

Almost one-third of the all PTSD patients ($n = 9$, 29.0 %) had at least one coexisting psychiatric disorders, whereas the control groups did not have any past psychiatric disorders (χ^2: 4, $p < 0.01$) (Table 1).

Table 1 Gender distribution, smoking status, history of psychiatric disorder, family history of psychiatric disorder, age, BMI, and biochemical measurements of the participants

	ES-PTSD ($n = 32$)	ES-non-PTSD ($n = 32$)	Healthy controls ($n = 38$)	Statistics	
	n (%)	*n* (%)	*n* (%)	χ^2	*p*
Gender					
Male	12 (37.5)	15 (46.9)	15 (39.5)	0.653	0.721
Female	20 (62.5)	17 (53.1)	23 (60.5)		
Smoking status					
Yes	11 (34.4)	14 (43.8)	13 (34.2)	0.842	0.656
No	21 (65.6)	18 (56.3)	25 (65.8)		
History of psychiatric disorder					
Yes	9 (29)	0	0	4	**<0.01**
No	23 (71)	32 (100)	38 (100)		
Family history of psychiatric disorder					
Yes	7 (22.6)	1 (3.1)	2 (3.5)	4	**0.032**
No	25 (77.4)	31 (96.9)	36 (96.5)		
	Mean ± SD	Mean ± SD	Mean ± SD	*F/t*	*p*
Mean age (years)	33.1 ± 12.4	30.6 ± 6.1	32.9 ± 11.8	0.512	0.601
Education (years)	7.3 ± 4.7	12.5 ± 4.7	13.2 ± 4.2	16.595	**<0.01**
BMI (kg/m^2)	24.4 ± 2.9	23.1 ± 2.7	23.7 ± 2.2	0.406	0.667
Malondialdehyde (nmol/mL)	20.7 ± 6.0[a]	17.7 ± 6.9	15.8 ± 7.5[a]	4.441	**0.014**
Paraoxonase (U/l)	61.5 ± 44[b]	70.4 ± 44.2	94.3 ± 65.9[b]	3.280	**0.042**
PCL-C	47.5 ± 15.03	22.9 ± 5.07	NA	8.757	
CGI	4.2 ± 0.7	NA	NA		

Bold values indicate statistical significance at $p < 0.05$

BMI: body mass index, ES-PTSD: earthquake survivors who have developed post-traumatic stress disorder, ES-non-PTSD: earthquake survivors who did not develop post-traumatic stress disorder, PCL-C: PTSD Checklist-Civilian Version, CGI-S: Clinical Global Impression-Severity of Illness, NA: nonassociated, χ^2: Chi-square value, *p*: statistically significant level, SD: standard deviation, F: statistical value of ANOVA, kg/m^2: kilogram per meter square, nmol/mL: nanomol per milliliters, U/: units per liter

[a] Post hoc Tukey analysis showed that difference in malondialdehyde levels is statistically significant between the groups ES-PTSD and healthy controls

[b] Post hoc Tukey analysis showed that difference in paraoxonase activity is statistically significant between the groups ES-PTSD and healthy controls

Family history

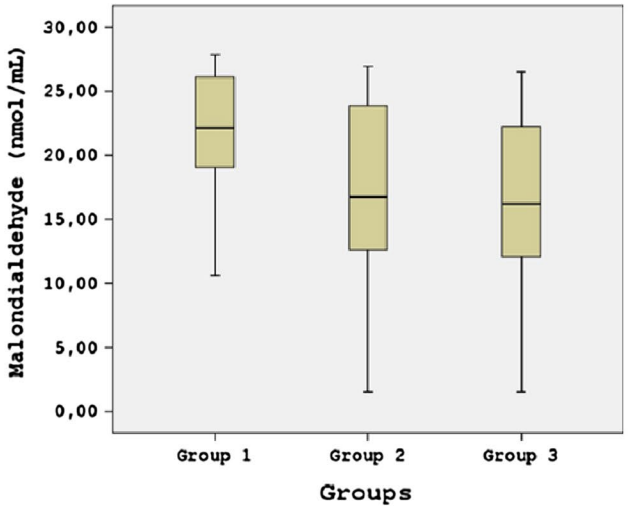
The overall frequency of family history of psychiatric disorders for each group (Groups 1, 2, and 3) was found to be 22.6 % ($n = 7$); 3.1 % ($n = 1$); and 3.5 % ($n = 2$), respectively (χ^2 :4 $p = 0.032$). Further, the family history of psychiatric disorder in the Group 1 was found to be significantly more frequent than those of the other two groups (Table 1).

Exposed to earthquake

Patients with PTSD showed significantly higher MDA levels and lower PON1 enzyme activities compared to those of controls who were never exposed to the earthquake (Table 1). Among earthquake survivors, patients that developed PTSD after the earthquake (Group 1) and participants without PTSD diagnosis (Group 2) did not show any statistically significant difference in terms of study variables.

The participants who did not develop PTSD after earthquake had higher MDA levels and lower PON1 when compared to the controls. However, these differences did not reach a statistically significant level (Table 1). Boxplots of MDA levels and PON1 activities of the Groups 1, 2, and 3 are shown in Fig. 1.

When we looked at the relationship between the clinical and demographic data and the biochemical parameters, MDA levels and psychological impact of earthquake, as determined by PCL-C, showed a positive correlation between survivors of earthquake ($r = 0.410$, $p = 0.02$).



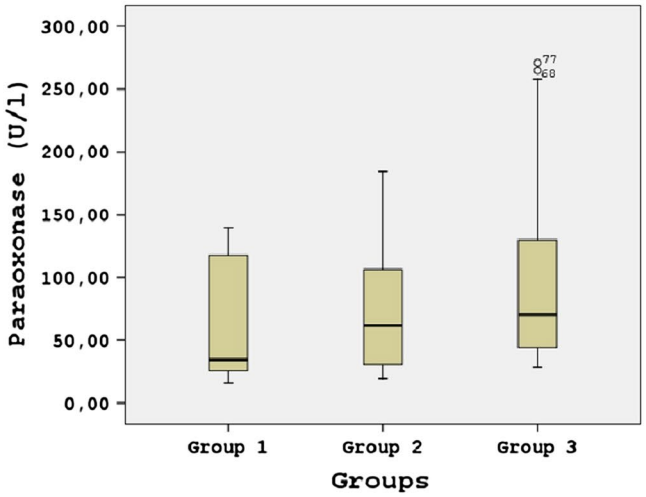


Fig. 1 *Boxplots* of malondialdehyde levels and paraoxonase activities of patient and control groups. Group 1: patient PTSD, Group 2: participants who were exposed to the trauma but had not developed PTSD, and Group 3: participants who have never been exposed to trauma and not diagnosed with PTSD

The average CGI-S scale score was 4.2 ± 0.7 points in Group 1. The average PCL-C scale score of Group 1 (PTSD patients) was significantly higher than that of the Group 2 (47.5 ± 15.0 and 22.96 ± 5.1, respectively; $t = 8.757$, $df = 62$, $p < 0.01$).

Discussion

As we know, oxidative stress has been implicated in response to stressful and traumatic life events, as well as the pathogenesis of numerous central nervous system (CNS) disorders, including psychiatric disorders [26–28]. Several approaches have been used to explain the etiology of oxidative stress in the brain [29]. Increasing evidence exists for a link between the HPA axis with the sympatho-adrenal-medullary systems and oxidative stress. An alternative explanation of the underlying mechanisms of oxidative stress is the activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympatho-adrenal-medullary systems, which causes the release of corticosterone together with catecholamines [30]. Consistent with previous explanations, oxidative stress parameters in the hippocampus have been found to be related to stress exposure and suggest increased production of free radicals in the hippocampus in response to stress [31–34].

Neuronal damage associated with oxidative stress has been implicated in numerous CNS disorders, including psychiatric disorders like schizophrenia, depression, and anxiety disorders [14, 35–39]. Interestingly, only a few studies have been focused on the relationship between oxidative stress and PTSD.

Although these survivors have not been diagnosed with trauma-related Axis I psychiatric disorder, it was easy to understand that the earthquake may have caused psychological distress on them. In the present study, a trend toward increased MDA levels and decreased PON1 enzyme activities was observed in earthquake survivors who did not develop PTSD. This seemed to be consistent with the above-mentioned studies that suggested increased oxidative stress secondary to psychological stress. These trends seem to reach a statistically significant level when underlying psychological distress resulted in psychiatric diagnosis such as PTSD. At this point, an alternative view can be made that PTSD diagnosis may add to the effects of trauma on serum MDA levels and PON1. Although it is nonsignificant, the differences between groups of earthquake survivors may indicate higher impact of PTSD development, on lipid peroxidation markers than trauma itself.

Our clinical and socio-demographic variables concurred with the previous findings in the literature. All three groups were similar in terms of their demographic variables and smoking status.

To the best our knowledge, this is the first study comparing the PON1 enzyme activities and MDA levels between patients who developed PTSD after the earthquake trauma. Recently, studies investigated the PON1 enzyme activities in psychiatric disorders and determined different results from our study. Similarly, earthquake survivors that did not develop PTSD showed also lower PON1 activity when compared to those of controls who were never exposed to earthquake. However, differences between these groups did not reach a significant level.

The other studies examined PON1 of psychiatric disorders, including schizophrenia, and showed a reduction in PON1 activity [40]. Major depression was accompanied by lowered PON1 activity, but bipolar disorder was not [41]. Ceylan et al. found PON1 activities in attention deficit hyperactivity disorder patients and showed that they were significantly lower than those of the controls [42, 43]. Bulut et al. [43] found decreased PON activity in generalized anxiety disorder patients, which suggests increased lipid peroxidation and oxidative stress in these patients. Similarly, PON1 activity was significantly lower in children and adolescent patients with obsessive compulsive disorder [44]. However, anxiety disorder patients were found to have no significant differences in PON1 activities compared to healthy controls in another study [45]. On the other hand, MDA levels of patients were reported to be positively correlated with the disease severity in social phobia [15]. Given these correlations, one may think that the psychological impact of trauma increases the oxidative mechanisms and the lipid peroxidation may be a strong contributor.

Recently, Tezcan et al. [17] investigated whether antioxidant enzyme activities (glutathione peroxidase, superoxide dismutase, and catalase) and MDA levels were associated with PTSD. However, they were not able to show any statistically significant difference between the PTSD patients and healthy controls in terms of the activities of some antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and the symptom severity of PTSD. However, they found that a positive correlation between the activities of some antioxidant enzymes (glutathione peroxidase and superoxide dismutase) and the symptom severity in PTSD patients. Additionally, they reported a positive correlation between symptom severity and MDA which did not reach statistically significant level [17].

Attari et al. measured the MDA levels and rates of hemolyzed blood cell in PTSD and healthy control groups and compared the indices for lipid peroxidation and antioxidant capacity, respectively. Finally, they showed higher lipid peroxidation (oxidative stress) rates and lower antioxidant capacity in the PTSD group when compared to control group [16].

On the other hand, a recent study examined oxidative damage markers in PTSD patients and concluded no relationship between them and PTSD [18]. Interestingly, that study recruited patients, survivors of Croatian war between 1991 and 1994, many years after their trauma; therefore, these patients may have chronic PTSD. As a result, chronic disorders (or conditions) like PTSD have been implicated in oxidative system, due to the so long period. In other words, PTSD diagnosis seems to add to the effects of trauma on serum MDA levels and PON1 enzyme activities. Serum MDA levels and PON1 may not serve as biochemical markers of earthquake trauma or impact of the traumatic event. However, they may serve as biochemical markers of PTSD diagnosis.

Our study reported a positive correlation between symptom severity and MDA, which did not reach statistically significant level. We discussed the relationship between oxidative stress and psychiatric disorders, including PTSD, by presenting the possible impact in the etiology and the different views that exist. As a result, oxidative stress may be implicated in chronic disorders like PTSD.

MDA is an end product of lipid peroxidation that is a well-known source of reactive oxygen species causing oxidative stress [36, 46]. Several studies show the relationship between oxidative stress and symptoms of PTSD like insomnia, numbing, avoidance, and dissociation or inability to recall important aspect trauma [47, 48]. Likewise, the higher MDA levels and lower PON1 activity were found in our study and may be a sign of increased oxidative stress in PTSD patients. Collectively with the previous literature, our results suggest that lipid peroxidation may be involved in PTSD patients and have an important role in the oxidative mechanism. It should be noted that associations between psychological stress and oxidative stress in clinical samples have also been reported.

Our results show higher MDA levels and lower PON1 enzyme activities and seem to support the results of these two previous studies. All together, this suggests an imbalance in the oxidative mechanism in PTSD patients. The major findings of our study are as follows:

1. Patients with PTSD have significantly higher MDA levels and lower PON1 enzyme activities compared to those of controls who were never exposed to earthquake.
2. There is a nonsignificant trend toward higher MDA levels and a lower PON1 enzyme activity in participants who did not develop PTSD after earthquake when compared to controls.
3. MDA level and psychological impact of earthquake as determined by PLP-C were positively correlated in the survivors of the earthquake. Finally, serum MDA levels and PON1 enzyme activities do not seem to serve as biochemical markers of trauma or traumatic event, namely earthquake, but may serve as biochemical markers of PTSD diagnosis.

Future studies are needed to expand this research to a larger patient sample size in order to define the clinical value of lipid peroxidation markers, especially MDA and PON1 in PTSD.

Limitations and strengths

Our study has some strengths and also methodological limitations related to logistical issues. To the best of our knowledge, this is the first population study of PON1 activity measured in PTSD patients. The mean PON1 enzyme activity of PTSD patients was significantly lower than those of the cases who have never experienced earthquake.

First limitation, small sample size of the study may be a hinderance to the differences between groups if they are present in reality. Second, it should be kept in mind that they are limited to the survivors of earthquake trauma and cannot be generalized to all PTSD patients when interpreting the results. Third, measurement of other lipid peroxidation markers, total oxidative stress, and total antioxidant capacity would be helpful to better understand the exact nature of oxidative mechanisms in these patients.

Compliance with ethical standards

Conflict of interest None.

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