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ORIGINAL ARTICLE

Serum thiol levels and thiol/disulphide homeostasis in gunshot injuries

Hasan Buyukaslan[1] · Umut Gulacti[2] · Mehmet Tahir Gökdemir[3] · Ramazan Giden[4] · Hakim Celik[5] · Özcan Erel[6] · Erman Mustafa Dörterler[7]

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Abstract

Background Gunshot injuries result in serious traumatic tissue damage due to high velocity of the bullet, deep penetration, and ballistic effect. Trauma is known to be related with oxidative stress. Serum thiol levels and disulphide/thiol homeostasis are novel oxidative stress biomarkers. In this study, we aimed to investigate serum thiol levels and disulphide/thiol homeostasis in injury patterns of patients admitted to the emergency department with a gunshot injury.

Method A total of 128 participants were included in the study. The participants were divided into two groups: the patient group (Group 1; $n=73$) and healthy controls (Group 2; $n=55$). Native thiol, total thiol, disulphide levels, disulphide/native thiol, disulphide/total thiol, and neutrophil-to-lymphocyte ratio (NLR) were measured. The Revised Trauma Scale (RTS) and Glasgow Coma Scale (GCS) scores were calculated.

Results Native thiol, total thiol, and disulphide levels were significantly lower in Group 1 ($p<0.001$). Disulphide/native thiol ratio, disulphide/total thiol ratio, and NLR were significantly higher in Group 1, compared to Group 2 ($p<0.05$). There was a positive correlation between thiol levels and RTS and GCS scores and NLR. Stepwise linear regression analysis showed that native thiol was an independent indicator of RTS and GCS scores. The receiver operating characteristic curve (ROC) analysis revealed that serum native thiol levels of ≤ 342.9 could predict gunshot injury with a sensitivity of 82% and a specificity of 77% (area under the curve = 0.853; 95% confidence interval 0.783–0.924).

Conclusion Our study results suggest that thiol–disulphide homeostasis is disrupted in patients sustaining gunshot injuries, and thiol levels decrease in correlation with the severity of trauma with a high sensitivity and specificity. As the level of native thiol is an independent predictor of the severity of trauma, reduced thiol levels may be of prognostic value in the early assessment of patients in the emergency room.

Keywords Thiol · Thiol–disulphide homeostasis · Gunshot injury · Emergency department · Neutrophil-to-lymphocyte ratio

Introduction

Gunshot injuries, which pose significant social and medical problems, are one of the leading causes of high mortality and morbidity in the hospitals related to trauma surgery worldwide [1]. Firearms cause damage in the entrance area and neighbouring tissues due to their high velocity and penetration. The damage is proportional to the energy transferred to the tissue, properties of the tissue, and how the

✉ Hasan Buyukaslan
buyukaslanh@gmail.com

[1] Department of Emergency Medicine, Harran University Education and Research Hospital, Şanliurfa, Turkey

[2] Department of Emergency Medicine, Adiyaman University Medical Faculty, Adiyaman, Turkey

[3] Emergency Department, Gazi Yaşargil Education and Research Hospital, Diyarbakir, Turkey

[4] Department of Emergency Medicine, Mehmet Akif İnan Education and Research Hospital, Şanliurfa, Turkey

[5] Department of Physiology, Harran University Education and Research Hospital, Şanliurfa, Turkey

[6] Department of Biochemistry, Ankara Atatürk Training and Research Hospital, Ankara, Turkey

[7] Department of Pediatric Surgery, Harran University Education and Research Hospital, Şanliurfa, Turkey

tissue distributes the energy, which causes severe injury in the tissues [2, 3].

It is well known that free oxygen radicals are generated and cause oxidative stress in trauma patients [4]. These oxygen radicals result in reversible or irreversible damage in biomolecules. Thiol is a compound containing sulphhydryl groups and one of the main antioxidant molecules scavenging free oxygen radicals generated due to trauma [4].

Thiols are critical antioxidant agents in humans, and thiols containing sulphur analog of alcohol are available as free or oxidized form in plasma [5]. The thiol plasma pool is mainly formed by protein thiols, including albumin, and to a lesser extent, low molecular mass thiols. The latter ones are mainly glutathione, homocysteine, cysteine, and γ glutamine [5]. In case of increased oxidative stress, thiol levels are reduced to neutralize the reactive oxygen species, in which case sulphhydryl groups of thiols play a key role [6]. In the presence of oxidative stress, reversible disulphide bond formation is seen between protein thiols and low molecular weight ones. These bonds may be reduced back to thiols to sustain thiol /disulphide homeostasis [7]. In the pathogenesis of a number of diseases, including diabetes, cardiovascular disease, and cancer, an abnormal thiol–disulphide homeostasis state has been demonstrated [8, 9].

Although there are several studies indicating the association between oxidative stress and trauma [10, 11], no study investigating thiol levels and disulphide/thiol homeostasis in gunshot injuries is available to date. Therefore, in the present study, we aimed to investigate the serum thiol levels and disulphide/thiol homeostasis in injury patterns of patients admitted to the emergency department with gunshot injury.

Materials and methods

A written informed consent was obtained from patients or their legal guardians. The study protocol was approved by the Ethics Committee of Harran University, Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A prospective case–control study was carried out in the emergency department of a tertiary care hospital. A total of 128 participants were enrolled in the study, and of these 73 patients with gunshot injuries (67 males, 6 females) comprised the patient group (Group 1), while 55 healthy subjects (49 males, 6 females) comprised the control group (Group 2). The patients with gunshot injury were divided into two groups: survival and non-survival. The demographic and clinical characteristics of the participating patients were recorded. Native thiol, total thiol, disulphide levels, disulphide/native ratio, and disulphide/total thiol ratio were compared between the groups.

Exclusion criteria for all participants (healthy individuals and patients) were as follows: conditions which may have potentially affected oxidative markers, such as chronic medical disorders (i.e. congestive heart failure, chronic obstructive lung disease, diabetes mellitus, chronic renal failure, hypertension, or malignancy), and coronary artery disease, peripheral vascular disease, and renal dysfunction; using medications such as sedative–hypnotic drugs or stimulatory substances; smoking; measurable blood alcohol concentrations or consumed alcohol prior to the study; using a specific diet; pregnancy or elevated human chorionic gonadotropin (hCG) levels, as assessed by a quantitative hCG blood test (β-hCG), and fall from a height with the intention of committing suicide. Those with blunt or other penetrating injuries were also excluded. None of the participants were using drugs known to affect lipid or lipoprotein metabolism. A special care was taken to rule out individuals who were taking anabolic drugs, diuretics, vitamins, or other antioxidants, such as vasoactive and beta-blocking agents.

The patients were provided with basic trauma life support at presentation and advanced trauma life support, when necessary. Their vital signs were monitored. The controls were healthy individuals selected randomly among the individuals who were admitted to hospital for checkup and in addition to other exclusion criteria did not have any known systemic diseases, and did not use any medications.

Blood sample collection

The blood samples of gunshot wound patients were taken immediately after arrival at the emergency department within 24 h of injury, and the blood samples of the controls were obtained in the morning, after a fasting period of 12 h. Blood samples collected from the patients and controls were put into plain tubes. The serum was separated from the cells by centrifugation at 4000 rpm for 5 min. Serum samples were stored at − 80 °C until analysis. Complete blood counts were measured from K_2EDTA samples using an autoanalyzer (Sysmex K-1000; Block Scientific, USA) within 5 min of sampling. Neutrophil and lymphocyte values were measured, and neutrophil-to-lymphocyte ratio (NLR) was calculated. Serum glucose, urea, creatinine, aspartate aminotransferase, and alanine aminotransferase levels were measured using a commercial kit (Abbott, Block Scientific, Bellport, New York, USA).

Assessment of thiols and thiol/disulphide homeostasis

Thiol/disulphide homeostasis was measured using a new and fully automatic analysis method developed by Erel and Neselioglu [8]. In this method, reducible disulphide bonds were first reduced to compose free functional thiol groups.

Unused reductant sodium borohydride was used up and extracted with formaldehyde, and all thiol groups containing native and reduced ones were determined after a reaction with 5,5′-dithiobis-(2-nitrobenzoic) acid. Half of the difference between native and total thiols ensured the dynamic disulphide changes. Once dynamic disulphide, native, and total thiol levels were measured, disulphide/native thiol and disulphide/total thiol ratios were calculated. Measurements were made using a Cobasc501 (Roche Diagnostics, Mannheim, Germany). Serum thiol/disulphide homeostasis values were presented in μmol/L [8].

Other measurements

The Revised Trauma Scale (RTS) and Glasgow Coma Scale (GCS) scores were calculated by a single health-care professional for each patient upon arrival at the emergency department. The RTS scores were calculated from the GCS score, systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate per minute. In haemodynamically stable patients, computed cranial tomography (CCT), ultrasonography (USG), radiographs, laboratory tests, and further assays were performed on each patient by a single investigator.

Statistical analysis

Statistical Package for Social Sciences for Windows version 18 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was used to analyze the distribution pattern of the variables. Continuous variables were expressed in mean [95% confidence interval (CI)], and categorical variables also expressed in number (%). Intergroup comparisons of normally distributed numerical variables were done with the Student's *t* test. The Mann–Whitney *U* test was used for intergroup comparisons of skewed distributed numerical variables. Categorical variables were analyzed using the Chi square and Fisher exact tests. The relations among the numerical variables were analyzed with the Pearson and Spearman correlation analysis. In addition, stepwise linear regression analysis was performed for independent variable. The receiver operating characteristic curve (ROC) analysis was also carried out. A *p* value less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of both the groups are shown in Table 1. The study included a total of 73 patients with gunshot injuries (Group 1) as the patient group and 55 age- and sex-matched controls (Group 2) as the control group. Of patients in Group 1, 67 were males and 6 were females, while 49 participants in Group 2 were males and 6 were females. The mean age of Group 1 and Group 2 was 30 years (27–33) and 29 years (26–32), respectively.

The measurements of SBP and DBP in both the groups are shown in Table 1. SBP and DBP were significantly lower and pulse rate was significantly higher in Group 1 compared to Group 2 ($p < 0.001$). The RTS and GCS scores were significantly lower in Group 1 than Group 2 ($p < 0.001$, Table 1). As an indicator of inflammatory reaction, NLR was significantly higher in Group 1. In addition, native thiol, total thiol, and disulphide levels were significantly lower in Group 1, compared to Group 2 ($p < 0.05$, Table 1; Fig. 1). In terms of dynamic thiol changes, disulphide/native thiol and disulphide/total thiol ratios were significantly higher in Group 1, compared to Group 2 ($p = 0.001$ for each, Table 1).

The distribution of gunshot injuries according to the injury site is shown in Table 2. Accordingly, the majority of patients had abdominal gunshot injuries, followed by chest, lower extremity, head and neck, upper extremity, chest + abdomen, and abdomen + lower extremity. Eight patients died due to intraabdominal organ injury ($n = 3$), intracranial injury ($n = 2$), chest wall injury ($n = 2$), and lower extremity fracture and vascular injury ($n = 1$). Table 3 shows the clinical and laboratory findings of the survivors vs non-survivors. The mean RTS and GCS scores were significantly lower in non-survivors, compared to survivors ($p < 0.001$ for each). There was no statistically significant difference in thiol levels between survivors and non-survivors, although native thiol, total thiol, and disulphide levels were significantly elevated in non-survivors ($p > 0.05$, Table 3).

The correlations of parameters related to RTS and GCS are presented in Table 4. Accordingly, both total thiol and native thiol levels were strongly and positively correlated with RTS and GCS scores (all $p < 0.001$). In addition, there was a weak positive correlation between disulphide levels and GCS scores ($r = 0.182$; $p = 0.040$), but not between RTS scores. In addition, there were negative correlations between disulphide/native thiol and disulphide/total thiol ratios and RTS and GCS scores. Similarly, there was a negative correlation between NLR and GCS ($p < 0.001$) and between NLR and RTS ($p = 0.002$). In addition, reduced thiol levels were negatively correlated with NLR (Table 5). Stepwise linear regression analysis showed that native thiol levels were independent predictors for GCS ($p = 0.003$) and RTS scores ($p = 0.026$) (Table 6). The receiver operating characteristic curve (ROC) analysis revealed that serum native thiol levels of ≤ 342.9 could be correlated with a sensitivity of 82% and a specificity of 77% (area under the curve = 0.853; 95% confidence interval 0.783–0.924) (Fig. 2).

Table 1 Demographic and clinical variables in the two groups

Variables	Group I ($n=73$)	Group II ($n=55$)	p value
Sex [male (%)]	67 (92)	48 (87)	0.403
Age (year)	30 (27–33)	29 (26–32)	0.990
SBP (mmHg)	107 (100–113)	120 (118–122)	**0.012**
DBP (mmHg)	64 (59–68)	74 (72–77)	**< 0.001**
Heart rate (bpm)	100 (94–106)	85 (83–87)	**< 0.001**
GCS	12 (12–13)	15 (15–15)	**< 0.001**
RTS	9 (9–10)	11 (10–11)	**< 0.001**
Glucose (mg/dl)	91 (89–94)	82 (79–85)	**< 0.001**
Urea (mg/dl)	27 (25–29)	26 (25–28)	0.664
Creatinine (mg/dl)	0.75 (0.71–0.80)	0.76 (0.71–0.81)	0.841
AST (U/I)	38 (37–38)	24 (22–26)	**< 0.001**
ALT (U/I)	39 (38–41)	31 (27–36)	**< 0.001**
Haemoglobin (mg/dl)	12.1 (11.4–12.7)	13.8 (13.5–14.2)	**< 0.001**
WBC (10^3/μL)	13.4 (12.0-14.9)	7.6 (7.4–7.9)	**< 0.001**
Neutrophil (10^3/μL)	10.4 (8.9–11.9)	4.5 (4.2–4.8)	**< 0.001**
Lymphocyte (10^3/μL)	3.3 (0.8–5.8)	2.5 (2.3–2.7)	**0.001**
NLR	7.9 (6.1–9.8)	2.1 (1.8–2.3)	**< 0.001**
Native thiol (μmol/L)	257.5 (231.6–283.5)	377.0 (364.8–389.1)	**< 0.001**
Total thiol (μmol/L)	285.5 (258.3–312.8)	410.6 (397.4–423.8)	**< 0.001**
Disulphide (μmol/L)	14.0 (12.7–15.3)	16.8 (15.5–18.2)	**0.004**
Disulphide/native thiol (%)	6.5 (5.4–7.7)	4.9 (4.1–4.8)	**0.001**
Disulphide/total thiol (%)	5.5 (4.8–6.2)	4.1 (3.8–4.4)	**0.001**

ALT aspartate aminotransferase, *AST* alanine aminotransferase, *RTS* Revised Trauma Score, *GCS* Glasgow Coma Scale, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *bpm* beats per minute, *WBC* white blood cell, *NLR* neutrophil/lymphocyte ratio

Discussion

The present study is the first to evaluate thiol levels, dynamic thiol changes, and their relationship with inflammation in patients with gunshot injuries. Our study results showed that thiol levels decreased in correlation with RTS and GCS scores in patients with gunshot injuries. As opposed to this decline, there was a significant increase in NLR. In terms of dynamic thiol changes, disulphide/native thiol and disulphide/total thiol ratios were significantly higher in the patient group. According to the stepwise linear regression analysis, native thiol levels were independent predictors for RTS and GCS in the present study.

Gunshots result in serious traumatic tissue damage due to high velocity of the bullet, penetration, and ballistic effects. Free radicals generated after trauma damage cell membrane, lipids in the structure of the cell membrane, proteins, and DNA, thereby leading to infections, multiple organ failure, and acute dysfunction of respiratory, renal, and cerebral systems [11, 14]. It is, therefore, of utmost importance to know thiol levels required to reduce free oxygen radicals and perform interventions for the survival of the patient after trauma and prevent the detrimental effects which may occur. Previous reports suggested an increase in reactive oxygen species associated with trauma and a decrease in antioxidant levels [11–13]. However, there are no data in the literature regarding thiols and their dynamic changes. Oxidative stress is an indication of tissue damage caused by increased reactive oxygen species. Thiols inhibit cellular and tissue damage, preventing the effects of reactive oxygen species on the cell membrane through lipid metabolism. The release of free oxygen radicals is stimulated in trauma patients after physical injury. The cascade of reactions results in cellular death through different mechanisms by increasing oxidative stress from the first day of injury [14]. In the present study, we, therefore, aimed to investigate altered thiol-mediated antioxidant defense mechanism in patients sustaining gunshot injuries.

A previous study examined the parameters of oxidative stress in multiple trauma patients and found a significantly decreased total antioxidant capacity in patients sustaining multiple traumatic injuries [10]. Oldham et al. [15] also reported a decrease in antioxidant levels in trauma patients. In addition, an experimental study in a rat model showed decreased antioxidant levels in animals sustaining severe cerebral trauma, hypotension, and hypoxia [16]. Lilios et al. [17] also found a significant decrease in antioxidant

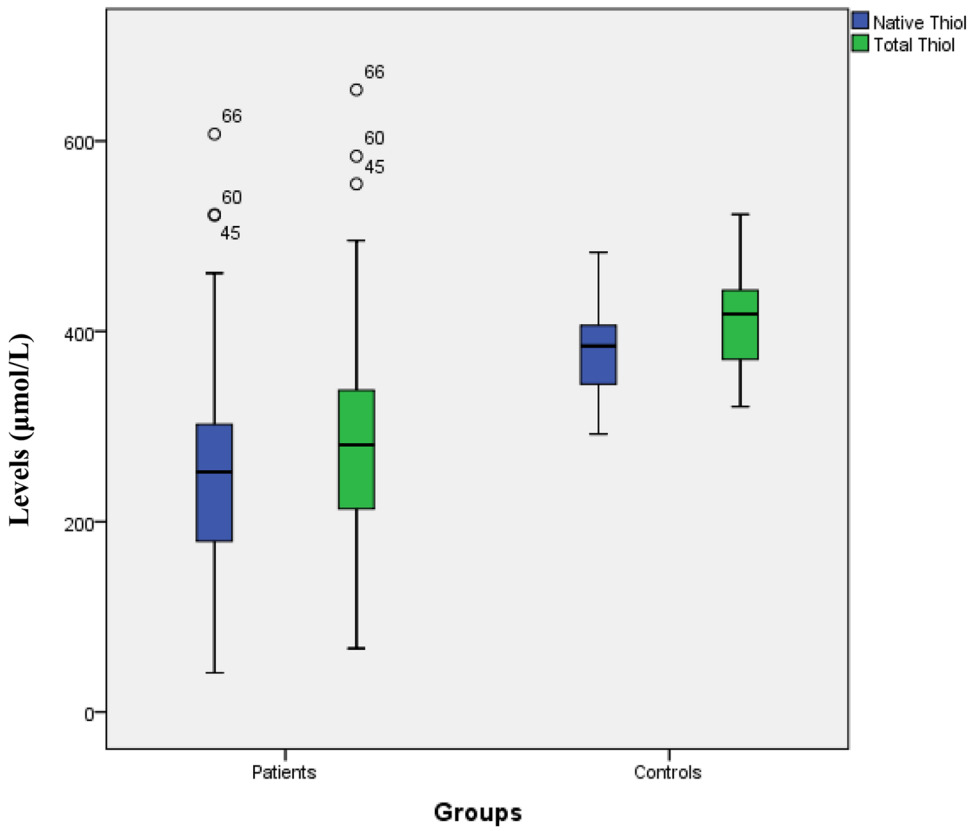

Fig. 1 Native thiol and total thiol levels showed statistically significant differences between both the groups

Table 2 Distribution of the cases according to the injury area

Injury location	*n* (%)	Survivors *n* (%)	Non-survivors *n* (%)
Thorax	18 (24.7)	16 (22)	2 (2.7)
Lower extremity	18 (24.7)	17 (23.3)	1 (1.5)
Head and neck	11 (15)	9 (12.3)	2 (2.7)
Abdomen	19 (26)	16 (22)	3 (4.1)
Upper extremity	3 (4.1)	3 (4.1)	0
Thorax and abdomen	3 (4.1)	3 (4.1)	0
Abdomen and lower extremity	1 (1.5)	1 (1.5)	0
Total	73 (100)	65 (89)	8 (11)

glutathione peroxidase levels within 3 days in pediatric patients with multiple traumatic injuries.

Oxidative stress is known to increase in trauma patients. Free radicals generated by oxidative stress are neutralized by non-enzymatic antioxidant thiols [18]. We suggest that the main reason for significantly lower thiol levels found in the present study was the attempt of the body to detoxify oxidative stress and free oxygen radicals generated by trauma.

In the present study, disulphide/native thiol and disulphide/total thiol ratios were significantly higher in the gunshot injuries group, compared to the control group. Disulphide/native thiol and disulphide/total thiol ratios were also found to be higher in the control group in the study by Dogru et al. [19] evaluating patients with ankylosing spondylitis associated with oxidation. Similarly, a study reported significantly higher disulphide/native thiol and disulphide/total thiol ratios in patients sustaining myocardial infarction [20]. It is well known that increased oxidative stress is accompanied by an acute inflammatory reaction in gunshot injuries [21]. The present study also found an increase in NLR, which is a marker of increased inflammation in this population. This increase was also negatively correlated with both native thiol and total thiol levels. Similar to our findings, decrease in thiol levels in parallel to increased inflammatory response was reported in patients with cardiac syndrome X [22].

The RTS is a common trauma scoring system in emergency departments for the classification of severity and outcome of trauma injuries. It combines respiratory rate and blood pressure data with GCS scores and is used for the assessment of outcomes of patients with multiple traumas [23]. There are several studies investigating the efficacy of scoring systems for severity of injuries, prognosis, and predicting mortality in gunshot wound patients [24–27]. In a study, RTS scores were found to be indicators of mortality for patients with trauma [28]. Kuhls et al. [29] also suggested that the RTS was an essential tool to

Table 3 Comparison of GCS and RTS scores between survivors and non-survivors with gunshot injury

Variables	Non-survivors	Survivors	*p* value
RTS	5 (3–6)	10 (9–10)	**< 0.001**
GCS	4 (3–6)	13 (13–14)	**< 0.001**
SBP (mmHg)	44 (18–70)	114 (110–118)	**< 0.001**
DBP (mmHg)	28 (12–43)	68 (65–71)	**< 0.001**
Native thiol (μmol/L)	263.3 (140.8–385.9)	256.8 (230.1–283.5)	0.887
Total thiol (μmol/L)	297.6 (172.1–423.1)	284.1 (256.0–312.8)	0.760
Disulphide (μmol/L)	17.1 (10.5–23.7)	13.6 (12.3–14.9)	0.103
Disulphide/native thiol, %	7.8 (2.8–12.8)	6.4 (5.2–7.5)	0.422
Disulphide /total thiol,%	6.4 (3.2–9.7)	5.4 (4.6–6.1)	0.382

RTS Revised Trauma Score, *GCS* Glasgow Coma Scale, *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Table 4 Correlations of related variables with GTS and RTS scores

Variables	GCS		RTS	
	r	*p* value	*r*	*p* value
Native thiol	0.423	< 0.001	0.331	< 0.001
Total thiol	0.422	< 0.001	0.322	< 0.001
Disulphide	0.182	0.040	0.111	0.210
Disulphide/native thiol	−0.202	0.022	−0.218	0.013
Disulphide/total thiol	−0.202	0.022	−0.218	0.013
NLR	−0.488	< 0.001	−0.277	0.002

RTS Revised Trauma Score, *GCS* Glasgow Coma Scale, *NLR* neutrophil/lymphocyte ratio

Table 5 Correlations between thiols and NLR

	Native thiol		Total thiol	
	R	*p* value	*R*	*p* value
NLR	−0.375	< 0.001	−0.384	< 0.001

NLR neutrophil/lymphocyte ratio

Table 6 Stepwise linear regression analyses of laboratory parameters for prediction of GCS and RTS scores

	GCS ($R^2 = 0.67$)		RTS ($R^2 = 0.39$)	
	β	*p* value	β	*p* value
Native thiol	0.258	0.003	0.197	0.026
Total thiol		0.313		0.141
Disulphide		0.313		–
Disulphide/native thiol		0.968		0.416
Disulphide/total thiol		0.898		0.308
NLR		0.104		0.269

RTS Revised Trauma Score, *GCS* Glasgow Coma Scale, *NLR* neutrophil/lymphocyte ratio

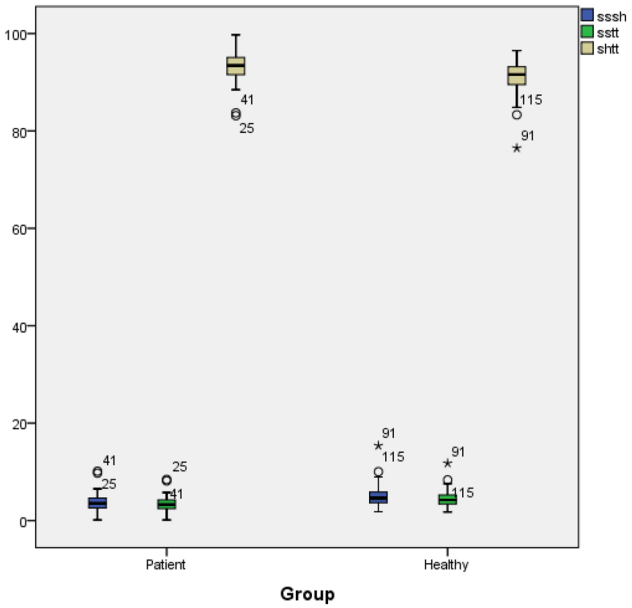

Fig. 2 Comparison of the SS/SH, SS/TT, and SH/TT ratios in the patient and control groups

determine the severity of the trauma patient. Similar to these studies, the mean RTS scores in the present study were significantly lower in non-survivors, compared to survivors. Furthermore, there was a strong correlation between the native thiol and total thiol levels and RTS scores. In addition, regression analysis showed that native thiol levels were independent predictors for RTS and GCS scores, suggesting that thiol levels which can be evaluated in patients sustaining gunshot injuries may offer a simple test tool providing information about the severity of injury. Based on these findings, we speculate that assessment of thiol levels can be used as an early prognostic marker in these patients.

Although evaluation of thiol levels in survivors vs non-survivors suggested higher native thiol, total thiol,

and disulphide levels in non-survivors, consistent with previous findings, the difference did not reach statistical significance. It can be attributed to the small sample size of non-survivors. Consistent with our findings, Lai et al. [30] also reported higher serum protein thiol levels in non-survivors from acute kidney injury, compared to survivors. Tsai et al. [31] reported a significantly higher plasma total antioxidant capacity in non-survivors, compared to survivors. Consistent with the literature, the present study found a higher antioxidant capacity in non-survivors. Higher levels of antioxidant enzymes in non-survivors seem to be a contradictory finding. However, the authors hypothesized that higher plasma total antioxidant capacity in non-survivors was a host response to excessive oxidative stress or a compensating mechanism for exhausted antioxidative components and excessive antioxidant defense, eventually leading to immune dysfunction and poor outcome [8, 32–34]. Due to the cross-sectional design of the present study, significant differences in the number of participants of both groups may be one of the main causes of these results.

Limitations

This study has some limitations. First, our sample size is small. Second, although the participants using supplemental vitamins were excluded, we were unable to standardize the antioxidant content of daily diet. Third, we were unable to measure other antioxidant parameters, such as lipid hydroperoxide, paraoxonase, and arylesterase. Fourth, patients sustaining gunshot injuries comprised those with injuries in different body sites such as the extremities, head, thorax, and lower extremity, and a subgroup analysis according to trauma sites was unable to be performed due to the limited number of patients in the subgroups. Fifth, we could not provide a time course of thiol level during the first 24 h, as all blood samples of participants were taken once. Finally, the patient number was comparatively low in this study and statistical power to compare thiol alterations between survivors and non-survivors was limited due to the small number of non-survivors among those with gunshot injuries.

Conclusions

In conclusion, our study results suggest that thiol–disulphide homeostasis, a marker of oxidative stress, is disrupted in patients sustaining gunshot injuries, and thiol levels decrease in correlation with the severity of trauma with a high sensitivity and specificity. As the level of native thiol is an independent predictor of the severity of trauma, reduced thiol levels may be of prognostic value in the early assessment of patients in the emergency room. However, further large-scale studies are required to confirm these findings.

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Compliance with ethical standards

Conflict of interest Buyukaslan Hasan, Gulacti Umut, Gökdemir Mehmet Tahir, Giden Ramazan, Celik Hakim, Erel Özcan, and Dörterler Mustafa Erman declare that they have no conflict of interest.

Informed consent A written informed consent was obtained from patients or their legal guardians.

Ethical approval The study protocol was approved by the Ethics Committee of Harran University, Faculty of Medicine. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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