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Evaluation of The Frailty Index and Thiol-Disulphide Levels in Geriatric Orthopedic Injuries

Evaluation of The Frailty Index

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Abstract:

Backround: One of the concepts recently discussed about old age is frailty. Frailty was found to be important in determining weakness and indulgence in the elderly. Frail older people are more likely to fall and experience related orthopedic trauma. Free oxygen radicals are known to cause oxidative stress in trauma patients. The aim of this study is to report the levels of frailty and thiol disulphide homeostasis and related factors in patients with geriatric orthopedic injury who presented to the emergency department.

Methods: This study included 82 patients aged 65 and over who were admitted to the Emergency Department of Ankara City Hospital in 2020 due to orthopedic trauma, and 38 people who presented for other reasons in a control group. FRAIL Frailty scale was used to evaluate frailty. In samples from patients' venous blood, native thiol and total thiol were analyzed.

Results: The average age of the patients was 78.48 ± 7.86 (min: 65-max: 99). Of the patients, 30.8% were in the prefrail group and 56.7% were in the frail group. In patient and control group comparisons, total thiol values in the patient group were significantly lower, and disulphide, ischemia-modified albumin, index 1 and index 2 values were significantly higher in the patient group compared with the control group. There were significantly more prefrail individuals (41.5%) among orthopedic trauma patients, and frail individuals (81.6%) in the control group. There was a significant weak negative correlation between body mass index and native thiol and total thiol values.

Conclusion: Oxidative stress is increased in patients with geriatric orthopedic injuries.

Key words: Geriatric patient, orthopedic injury, oxidative stress, frailty

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INTRODUCTION

Aging is a complex condition that is difficult to define. It is a universal process that involves a progressive decline in physiological processes and a permanent decrease in all functions over time.[1] Individuals older than 65 years are defined as elderly. Old age is divided into three stages; the first stage involving ages 65-74 is the young old stage, the second stage involving ages 75-84 is the middle old stage, the third stage involving ages 85 and over is the old old stage.[2,3] Aging varies across individuals. In the evaluation of aging, not only age but the functional capacity of the individual should also be considered. In the evaluation of elderly patients, planning must be performed by assessing whether or not patients are healthy.[4] Frailty is one of the concepts discussed in relation to old age in the recent times. Frailty was found to be important in determining weakness and indulgence in the elderly. The rise in the elderly population, and the presence of multiple diseases in elderly individuals increase the prevalence of frailty in the population. Along with aging, chronic diseases increase and the medication burden shows a parallel rise.[5] While it varies between 10-25% in the general population older than 65 years, it reaches up to 30-45% above 85 years of age.[6-8] Trauma is an important cause of mortality in young adults worldwide. Rates of trauma-related causes of morbidity and mortality vary between 7% and 45%.[9] Although trauma is a significant condition for all age groups, trauma care for the elderly has a special status due to the decrease in their metabolic and physiological capacity.[10] The participation of the elderly in the daily life and social life increases their risk of experiencing trauma.[11]

As in many other patient groups, free oxygen radicals are also known to cause oxidative stress in trauma patients. Further, a review of the literature reveals that frail and prefrail conditions are associated with elevated oxidative stress and reduced antioxidant activity. Thiols are known as mercaptans and are organic compounds that are made up of a sulphur atom and a hydrogen atom attached to a carbon atom, which involve a sulfhydryl (-SH) group.[12] Disulphide bonds found in these molecules can be re-reduced to thiol groups. Because of this property, thiol/disulphide homeostasis is a sustainable reaction.[13] Thiols comprise a large portion of the total antioxidants found in our bodies and exert considerable resistance against reactive oxygen molecules.[14,15] Thiols in plasma have either prooxidant or antioxidant physiological effects and are generally accepted to be antioxidants.[16] They also play a critical role in programmed cell death, detoxification, antioxidant protection and the regulation of cellular enzymatic activity.[17] Measuring serum levels of thiol may indirectly indicate antioxidant protection.[18] Therefore, plasma total thiol (TT), native thiol (NT) and disulphide levels have gained a wider use in routine clinical diagnosis and the monitoring of certain diseases and metabolic disorders.[19] This study assesses frailty levels and thiol disulphide homeostasis levels of patients with geriatric orthopedic injuries who presented to the Emergency Department of Ankara City Hospital to investigate whether there exist differences between the patient and control groups.

MATERIALS AND METHODS

This study was conducted on individuals older than 65 years who presented to the Emergency Department of Ankara City Hospital in 2020 (March-May) with orthopedic injuries. This is a non-randomized clinical trial. The minimum sample size required for this study was determined as 87 based on the sample size analysis conducted at 80% power and a 95% confidence interval (20). One-hundred-and-twenty patients were enrolled. Of these, 82 were patients with orthopedic trauma and 38 were control subjects.

Inclusion criteria:

- Aged 65 or older with an isolated orthopedic injury
- Voluntary participation

Exclusion criteria:

- Multi-trauma patients
- Chest trauma patients

- Head trauma patients
- Non-consent to participation
- Cerebrovascular disease
- Chronic kidney disease
- Rheumatoid Arthritis
- Chronic liver disease
- Acute-chronic infection
- Presence of malignancy
- Antioxidant medication use
- Smoking
- Alcohol use
- Parkinson's, Alzheimer's disease
- Aged less than 65 years

Measurements

a) Frail Frailty Scale

The FRAIL scale was used to determine the patients' frailty states. The validity-reliability study of the FRAIL scale in Turkish was conducted in 2017 by Muradi and colleagues (20). This scale has 5 components: Fatigue, Resistance, Ambulation, Illness, and Loss of Weight. Each component is scored as 0 or 1. The total score varies between 0 and 5. Scores are evaluated as follows; 0: normal, 1-2: prefrail, 3-5: frail.[20]

b) Thiol Disulphide Homeostasis (TDH)

Patients' venous blood samples were analyzed for thiol-disulphide levels. The samples were analyzed using a Roche Cobas C 501 device, in the Emergency Biochemistry Laboratory of Ankara City Hospital. The samples were stored in a refrigerator, at -80 degrees, for 3 months. All samples were analyzed when the sample size was met. Collected blood samples were analyzed for NT, TT and disulphide levels. The indices of these measurements were calculated as follows:

Index 1= (disulphide/native thiol) x 100

Index 2= (disulphide/total thiol) x 100

Disulphide= (total thiol-native thiol) / 2

c) Measurement of Thiol-Disulphide Homeostasis Parameters

Thiol disulphide homeostasis tests were performed according to the automatic spectrophotometric method developed by Erel and Neselioglu. Firstly, disulphide bonds were reduced with sodium borohydride in order to produce free functional thiol groups. Unused reducer sodium borohydride was removed using formaldehyde in order to prevent the reduction of DTNB (5,5'-dithiobis-2-nitrobenzoic acid). Following reaction with DTNB, all thiol groups, including reduced and native thiol groups were determined. Half of the difference between total thiols and native thiols is equal to the amount of dynamic disulphide. Following the determination of the amounts of native thiol, total thiol, and disulphide; disulphide/total thiol (SS / SH + SS), disulphide/native thiol (SS / SH), and native thiol/total thiol (SH / SH + SS) percent ratios were calculated.[17,21]

Statistical Analysis

Data analyses were conducted using the SPSS 22.0 program. The Kolmogorov Smirnov test was used as a test of normal distribution. Qualitative data were presented as frequency and percentages, and quantitative data as mean, standard deviation, and median values. Data analyses used the chi-square test, Mann-Whitney U test, student's t-test, Kruskal Wallis test, One Way ANOVA, and Spearman correlation analysis. $p<0.05$ was considered significant.

RESULTS

The mean age of the 87 trauma patients who presented to the emergency department and 38 individuals in the control group was 77.87±7.80 (min:65-max:95). Sociodemographic characteristics of the patients are provided in Table 1.

Tablo 1. Sociodemographic characteristics	
Characteristic	**n/(%)**
Group patient/control	82(68.3) / 38(31.7)
Gender male/female	61(50.8) / 59(49.2)
Age 65-74/75-84/85 and older	40(33.3) / 47(39.2) / 33(27.2)
Frailty normal/prefrail/frail	15(12.5) / 37(30.8) / 68(56.7)
Trauma site pelvis/lower extremity/upper extremity	42(51.2) / 27(32.9) / 13(15.9)
Chronic disease yes/no	24(20.0) / 96(80.0)

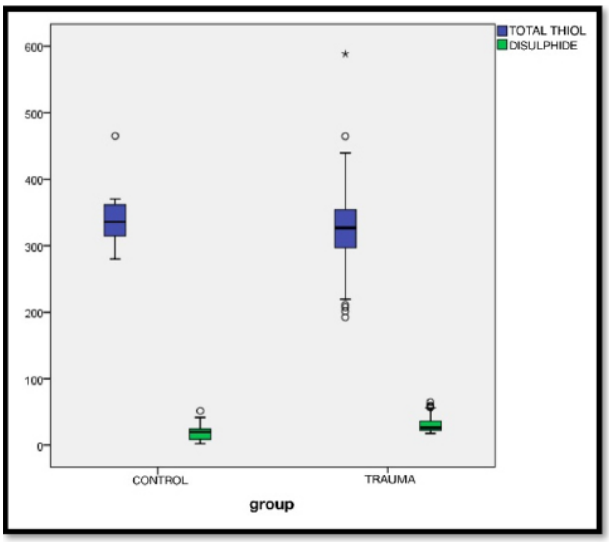
Twenty-five per-cent of these patients had quit smoking, and 75% never smoked. Of the patients, 5.8% were immobile, while 59.2% were mobile enough to fulfill basic needs and 34% showed a normal level of mobility. At least one chronic disease was present in 80% of the patients, and 80% of the patients used at least one regular medication. Comparison of frailty states according to various characteristics is provided in Table 2.

Table 2. Comparison of frailty states				
	Frailty group (n/%)			
Group	**Normal**	**Prefrail**	**Frail**	**p**
Patient	11 (13.4)	34 (41.5)	37 (45.1)	**<0.001**
Control	4 (10.5)	3 (7.9)	31 (81.6)	
Trauma site				
Pelvis	5(11.9)	15 (35.7)	22 (52.4)	
Lower extremity	4 (14.8)	9 (33.3)	14 (51.9)	**0.046**
Upper extremity	2 (15.4)	10 (76.9)	1 (7.7)	
Gender				
Male	10 (16.4)	18 (29.5)	33 (54.1)	0.423
Female	5 (8.5)	19 (32.2)	35 (59.3)	
Age				
65-74	7 (17.5)	15 (37.5)	18 (45.0)	
75-84	5 (10.6)	15 (31.9)	27 (57.4)	0.311
85 and over	3 (9.1)	7 (21.2)	23 (69.7)	

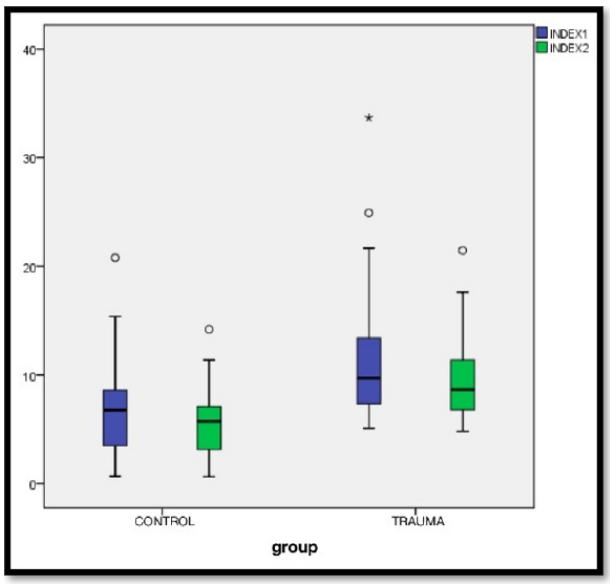
It was found that trauma and control groups were significantly different with regard to frailty states, and that, when the trauma site was considered, more patients with pelvic orthopedic traumas were in the frail group. There were no differences between frailty states in terms of gender and age. Both in the control group and in the patient group, the number of individuals who showed normal physical activity levels was significantly lower in the frail group compared with normal and prefrail groups ($p<0,05$). Comparison of patient and control groups with regard to blood thiol levels and the calculated indices is provided in Table 3.

Table 3. Comparison of TDH (Thiol Disulphide Homeostasis) between trauma and control groups					
	Trauma		**Control**		
	X±S.D.	**Median**	**X±S.D.**	**Median**	**p**
Native Thiol (umol/L)	322.4±69.6	305.8	309.3±83.8	305.6	0.450
Total Thiol (umol/L)	372.6±63.7	362.5	350.8±88.0	339.4	**0.045**
Disulphide (umol/L)	19.0±12.6	18.6	30.7±10.8	26.8	**<0.001**
Albumin (g/dl)	3.1±0.66	2.9	3.5±0.98	3.7	0.099
Index 1	6.4±4.8	5.6	10.6±5.0	9.2	**<0.001**
Index 2	5.2±3.4	4.9	9.0± 3.3	8.2	**<0.001**

The comparison of trauma and control groups revealed that total thiol levels were significantly lower and disulphide, index 1, index 2 levels were significantly higher in the trauma group compared with the control group. Distributions of TT, disulphide, index 1, index 2 levels in the patient and control groups are presented in the graphs below.



Graph 1. Total thiol and disulphide levels of trauma and control groups



Graph 2. Index 1 and Index 2 values of trauma and control groups

Blood thiol levels by frailty state are presented for patients in the trauma group in Table 4.

Table 4. Comparison of TDH (Thiol Disulphide Homeostasis) across frailty states (trauma group)							
	Normal		**Prefrail**		**Frail**		
	X±S.D.	**Median**	**X±S.D.**	**Median**	**X±S.D.**	**Median**	**p**
Native Thiol	291.1±64.7	283.7	304.7±86.4	295.5	319.0±87.0	310.1	0.629
Total Thiol	332.6±67.9	339.8	344.7±88.4	336.0	361.8±93.2	339.0	0.637
Disulphide	30.7±7.1	29.2	30.0±13.0	23.8	31.3±9.6	30.6	0.207
Albumin	3.5±0.68	3.8	3.7±1.0	3.7	3.4±1.0	3.2	0.723
Index 1	11.1±4.1	9.7	10.7±6.3	8.2	10.3±4.0	9.7	0.366
Index 2	9.5±2.9	8.6	9.0±3.9	7.5	8.9±2.8	8.5	0.398

The comparison of blood thiol levels of patients in the trauma group across frailty categories did not reveal a significant difference. Correlations between body mass index and blood thiol levels are provided in Table 5.

Table 5. Correlations between BMI (Body Mass Index) and TDH(Thiol Disulphide Homeostasis) levels

	BMI	
	r	**p**
Native Thiol	-0.188	**0.040**
Total Thiol	-0.198	**0.030**
Disulphide	-0.035	0.701
Albumin	0.073	0.425
Index1	0.092	0.319
Index2	0.102	0.269

Body mass index showed a significant weak negative correlation with native thiol and total thiol levels.

DISCUSSION

In this clinical study, the comparison of trauma and control groups showed that total thiol levels were significantly lower in the trauma group compared with the control group; and that disulphide, index 1 and index 2 levels were significantly higher in the patient group. The oxidant burden was determined to be significantly higher in the trauma group. It was found that the number of prefrail and frail individuals was significantly higher among patients with orthopedic trauma, and that the control group had significantly more frail individuals than those with a frailty state evaluated as normal. The literature reports that frailty can occur due to complex conditions involving a multitude of factors such as unintentional weight loss, reduced appetite, cognitive impairment, depression, sarcopenia, osteopenia, activation of inflammatory and coagulation systems, increase in coagulopathy and inflammatory markers, and activation of catabolic cytokines.[22] According to the information existing in the literature, frailty fractures occur at increasing rates, producing considerable economic and societal effects. Identifying the patients who are at risk, initiating effective treatment of metabolic bone disease and comprehensive planning of treatment protocols to reduce future fractures constitute an indispensable component of this process.[23] Since osteoporosis and osteoporotic fractures maintain their status as an important public health problem worldwide, the concept of osteoporosis-related frailty in the elderly is gaining wider acceptance and has prompted new studies that assess frailty in osteoporotic fractures. The assessment of frailty levels in the elderly appears to be quite useful in the evaluation and management of osteoporosis and osteoporotic fractures and the related decisions, in the context of both clinical research and health policy.[24] Osteoporosis is associated with elevated oxidative stress and free radical levels. In elderly frail individuals, elevated levels of free oxygen production were found to overcome the natural antioxidant defense mechanisms, expose individuals to hyperoxidant stress, and thus, lead to osteoporosis. Improving the antioxidant levels of these individuals can protect their bones against osteoporosis and also help accelerate the healing of fractured bones.[25]

Another important result obtained in the present study is that frail and prefrail states were more common in patients with lower extremity and pelvic traumas; while frail states were less common in patients with upper extremity traumas. Fall-related lower extremity and pelvic fractures are a common problem with significant impact on patients, caregivers, health service providers and the society. The largest burden is caused by hip fractures and

although the surgery is usually successful, many patients do not fully recover. Most individuals who sustained a hip fracture do not regain their previous activity and mobility levels, and thus, there is a higher risk of falling. Many of these patients also show higher levels of dependence; approximately 10% fail to return to their previous states.[26-28] Based on this, we can state that these fractures make the patients frailer; and that these frail states constitute a risk factor for many complications such as fractures etc. Optimizing recovery after lower extremity fractures and preventing further falls have the potential to decrease the burden on the individuals and the society.[29-31] Considering that, in the present study, frail and prefrail states were more common among patients with lower extremity and pelvic traumas; preventing the exposure of these patients to trauma, eliminating the factors that facilitate trauma and the occurrence of fractures, and in the case that fractures occur, ensuring fracture healing and regaining of previous functioning would improve the long term outcomes in these patients. As falling continues to be an important problem in the elderly populations worldwide, studies have evaluated the effects of exercise programs on avoiding further falls in fracture patients. Studies conducted by Bischoff-Ferrari and colleagues, Orwig and colleagues, and Sherrington et al. suggest that exercise programs with carefully constructed details for elderly patients with fall events should be devised.[3,33] The fact that frail and prefrail states were more common in patients with lower extremity and pelvic trauma in the present study reminds us once again that patients in these groups require a multidimensional approach. On the other hand, in our study, the number of those with normal physical activity levels were lower in the frail group than in normal and prefrail groups, both in the control and the patient group. Based on these findings, we can state that precautions taken against frailty would reduce these fractures, which have devastating effects, and that reducing these fractures would, in turn, prevent frailty.

According to literature data, frail and prefrail states are related to elevated oxidative stress and reduced antioxidant activity.[34] One of the important results of our study is that oxidative stress parameters were higher and the antioxidant status was decreased in the elderly orthopedic trauma group compared with the control group: it was found that total thiol levels were significantly lower in the patient group, and disulphide, index 1 and index 2 levels were significantly higher in the patient group compared with the control group. Oxidative stress is generally defined as a consequence of an imbalance between oxidant production and oxidant scavenging by protective mechanisms such as antioxidants. Cells that have a central role in fracture healing may be influenced, causing osteoblastogenesis to decrease, but osteoclastogenesis, which results in a net decrease in bone density, to increase. Additionally, intrinsic oxidative stress may lead to problems in bone reformation due to osteocyte apoptosis resulting from irreversible cell injury caused by excessive toxic radicals.[35,37] The dynamic thiol disulphide homeostasis state has critical roles in antioxidant production, detoxification, signal transduction, apoptosis, regulation of enzymatic activity, and transcription factor and cell signaling mechanisms.[38,39] Moreover, an increasing number of findings suggest that it has a more significant role than previously thought in a variety of diseases. Therefore, determining dynamic thiol disulphide homeostasis can provide valuable information regarding various normal and/or abnormal biochemical processes.[40,41] Accordingly, our study performed these measurements and reached highly significant results in the patient group compared with the control group. In addition to physical interventions that aim to prevent fractures and/or ensure recovery and return to previous functioning states in patients with orthopedic injuries; these data will strengthen our position in coping with complicated and multifactorial conditions such as frailty. As in many patient groups, free oxygen radicals are known to induce oxidative stress in trauma patients.[41,42] In the present study, the comparison of patient and control groups revealed that total thiol levels were significantly lower and disulphide, index 1 and index

2 levels were significantly higher in the patient group compared with the control group. Also, our study determined a significant weak negative correlation between body mass index and NT, TT levels. We can interpret these findings better if we remember that, according to literature data, obesity and oxidative stress are related, and further, that obesity is a risk factor for frailty.[43,44] We can state that both the oxidative stress levels and the frailty levels of these patients would be more favorable when the body mass index conforms to ideal levels.

In a study by Iskender and colleagues that investigated thiol homeostasis in patients with traumatic bleeding and hemorrhagic shock who presented to the emergency department and a control group; significant differences were determined, in descending order of significance, in NT, TT, disulphide, disulphide/NT, disulphide/TT, and NT/TT levels. It was found that the patient group had significantly lower native thiol, total thiol, native thiol/total thiol ratios and disulphide levels, and significantly higher disulphide/native thiol, disulphide/total thiol ratios.[42] Similar results were obtained in the present study, showing significantly lower total thiol levels and significantly higher disulphide, index 1 and index 2 levels in trauma patients compared with the control group. It can be seen that trauma modifies the thiol homeostasis. In patients with serious trauma, the amount of oxidative stress generally depends on various parameters such as total antioxidant capacity and lipid peroxidation. It was reported that monitoring the oxidant-antioxidant ratios could be a useful tool in the evaluation of the level of oxidative stress, inflammation, the severity of injury and the potential effectiveness of treatment.[45,46] In agreement with the literature data, it was found in the present study that oxidant capacity increased and antioxidant capacity decreased in trauma patients. Increasing the total antioxidant capacity in patients who present with trauma can be considered in order to improve the outcomes of treatment. A better understanding of fracture and oxidative stress mechanisms may help define the role of oxidative stress following a fracture, and perhaps, determine the contribution of antioxidants to fracture healing more clearly.[47] In the early period after a fracture, reactive oxygen species (ROS) are produced under inflammatory and ischemic conditions due to vascular and soft tissue injury, and this leads to cell death. Generally, during fracture healing, such injuries can be prevented to a great extent through the protective mechanisms and functions of antioxidant enzymes. However, excessive toxic radicals produced due to intrinsic oxidative stress can cause irreversible damage to cells associated with bone repair in the fracture healing process. Therefore, individuals with Type-2 diabetes mellitus, osteoporosis, alcohol intake, and heavy smokers are at risk for defective fracture healing due to high oxidative stress.[48] Preventing these disorders and abnormal conditions would have a positive effect on fracture healing and offer patients a healthier life by averting frail states.

We report the low number of controls in the study and the fact that the controls were recruited from individuals who presented to the emergency department as the limitations of this study. The results of this study show that oxidative stress is elevated in patients with orthopedic trauma. Prefrailty and frailty are higher among trauma patients. Improving oxidative stress, frailty and the conditions that induce frailty can have a favorable effect on the outcomes of frail patients with orthopedic injuries. All geriatric trauma patients should be evaluated multidimensionally with a perspective to prevent frailty and its negative consequences.

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