

The Importance of Thiol/Disulfide Homeostasis– and Ischemia–Modified Albumin Levels in Acute Coronary Syndrome and Their Relationship with Angiographic Scoring Systems

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ABSTRACT

Objective: The objective of this study was to investigate the differences in thiol/disulfide homeostasis- and ischemia-modified albumin (IMA) levels that are known to be associated with oxidative damage in patients with acute coronary syndrome between ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction/unstable angina pectoris (NSTEMI/USAP) groups and their relationships with angiographic scoring systems.

Methods: A total of 142 patients were included in this study, with 49 in group 1 (STEMI) and 93 in group 2 (NSTEMI/USAP). Thiol/disulfide homeostasis was determined using a recently developed novel method. We investigated whether thiol/disulfide homeostasis and parameters such as IMA, troponin I, and creatine kinase MB fraction levels were associated with Gensini, and Syntax I and II scores, which are angiographic scoring systems.

Results: The native and total thiol levels were found to be statistically significantly lower in the STEMI group than in the NSTEMI/USAP group (both, $p < 0.05$). The serum IMA levels were statistically significantly higher in group 1 (0.59 ± 0.12 vs 0.46 ± 0.23 absorbance units, $p < 0.05$). A significant positive correlation was found between the IMA and peak troponin I levels.

Conclusion: Thiol/disulfide homeostasis was shifted in favor of disulfide in the STEMI group, indicating a significant correlation between increased myocardial damage and disulfide. Similarly, the significantly higher IMA levels and positive correlation between IMA and peak troponin I in the STEMI group indicate its vulnerability in the infarcted myocardium area in addition to its vulnerability known in ischemia.

Keywords: Thiol/disulfide homeostasis, ischemia-modified albumin, acute coronary syndrome

INTRODUCTION

Irreversible endothelial cellular damage occurs with insufficient enzymatic and nonenzymatic antioxidant mechanisms against the effects of oxidative damage occurring with reactive oxygen species (ROS) (1). This is the most important cause of atherosclerosis (2). Increased oxidative stress increases both the incidence of coronary artery disease (CAD) and the vulnerability of an existing stable plaque, increasing the risk of the acute coronary syndrome (ACS) (3-5). Thiol groups in cysteine, homocysteine, glutathione, albumin, and other proteins, which are constituents of the antioxidant defense mechanism, are oxidized by ROS, giving rise to reversible disulfide bonds (6). The disulfide

bonds can be reversibly reduced to thiol groups by several antioxidants; in this way, the thiol/disulfide homeostasis is maintained (7, 8). Dynamic thiol/disulfide homeostasis has a crucial role in redox reactions such as antioxidant defense, oxidation of proteins, and apoptotic activity of enzymes. Abnormal thiol/disulfide homeostasis levels are involved in the pathogenesis of many diseases. Many studies are investigating the existence and prevalence of CAD and disulfide and thiol levels and homeostasis in patients with ACS (9-11). The N-terminal amino end of the albumin molecule is the binding site of metal ions such as Co^{+2} , Ni^{+2} , and Cu^{+2} . In oxidative stress, in cases of exposure to acidosis, hypoxia, free iron, and copper, this N-terminal

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end is modified, and its ion-binding feature decreases (12). This modified form of albumin is named ischemia-modified albumin (IMA) (13). The serum IMA level is known to increase in ACS (14). The IMA level can be used as a cardiac biomarker in clinical practice both by increasing in the early period of ischemia and by its high levels up to 6–12 hours in myocardial infarction (MI) (15–18). Studies have been conducted in patients with CAD and ACS (19–21). Thiol/disulfide homeostasis has been measured since 1979 only in one direction, but the novel method recently developed by Erel and Neselioglu (8) allows the levels of both variables to be measured separately and jointly.

In this study, we investigated the differences between the two groups as ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction/unstable angina pectoris (NSTEMI/USAP) in terms of both dynamic thiol/disulfide homeostasis parameters with a method developed by our researchers and serum IMA levels associated with increased myocardial damage in ACS patients. In addition, we investigated their correlations with Gensini, and Syntax I and II scores, which are angiographic scoring systems showing the prevalence and severity of CAD.

METHODS

The study was designed as a prospective single-center study. Group 1 consisted of 49 patients with ST-STEMI who were immediately taken to the catheter laboratory, and group 2 included 93 patients admitted in the coronary intensive care unit with NSTEMI and unstable angina pectoris (USAP) who then underwent coronary angiography. Both groups were informed of the procedure before the study, and written consent was obtained. The ethics committee approved the study protocol. The study complied with the Declaration of Helsinki. The patients' baseline characteristics, age, sex, and cardiovascular risk factors (hypertension [HT], diabetes mellitus [DM], hyperlipidemia [HL], obesity, smoking, family history, etc.), and previous history of percutaneous or surgical revascularization were recorded. In addition to the Gensini and Syntax anatomical scores, the Syntax II (SS II) score was calculated after coronary angiography. The Gensini score was computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its geographic importance (22). Each lesion was 1.5 mm in diameter, and 50% stenosis was scored using the online SS Calculator

version 2.1 (www.syntaxscore.com). Fluoroscopic visualizations were evaluated by two experienced cardiologists who were not aware of the clinical specifications of the patients. In case of disagreement, the opinion of a third observer was received, and the final decision was made by consensus. To calculate the SS II score, ejection fraction (EF) was studied using the Simpson method with echocardiography, and GFR values calculated with Cockcroft Gault formula were recorded. In addition, patients were evaluated by the thoracic clinic for chronic obstructive pulmonary disease (COPD), and those with COPD and peripheral vascular disease (PVD) were recorded (23–25).

Patients with severe systolic heart failure (EF < 40%), those with end-stage renal failure or nephrotic syndrome, severe liver disease, active infection, known rheumatological or hematological disease, and histories of cerebrovascular stroke and cancer were excluded from the study.

Laboratory Analysis

Venous blood samples were collected on admission or within the first 24 hours from patients with ACS into both EDTA-containing and serum-separating tubes. The samples were then centrifuged at 1500 rpm for 10 minutes to separate the plasma and serum. After centrifugation, the separated plasma and serum samples were frozen at -80°C until analysis. Samples with significant absorptions in the red region of the visible spectrum, which equates to extracellular hemoglobin levels of >0.3 g/l, were excluded from the study analyses.

Thiol/disulfide homeostasis parameters were determined with a novel method as described previously [8] by a spectrophotometric method using an automatic clinical chemical analyzer (Roche, Cobas 501, Mannheim, Germany). Serum IMA values were measured using the colorimetric method described by Bar-Or et al. (26) and IMA results were reported as absorbance units (ABSU). The albumin level was measured using the bromocresol green method. Creatinine (Cr) level and creatine kinase MB fraction (CK-MB) were measured using an enzymatic colorimetric method. Other laboratory parameters were measured with the Abbott Chemistry Analyzer. Cardiac troponin I (cTnI) level was measured with the Abbott Architect.

Statistical Analyses

A sample size of $n=48$ per group was required to provide 80% power to detect a difference in mean level with a significance of 0.001 (two-sided α). The normal distribution of the data was tested using a one-sample Kolmogorov-Smirnov test. Continuous variables are presented as mean \pm SD. Categorical variables are presented as counts. The statistical comparisons were performed using the two-sided Student *t* test. Categorical variables were compared using the Chi-square test or Fisher exact test for small samples. The Pearson correlation analysis was used for the numerical data. A multivariate logistic regression model was used to determine the effect of thiol/disulfide homeostasis and IMA levels on the angiographic scores. *P* values < 0.05 were considered statistically significant. The statistical analyses were performed using the Statistical Package for Social Sciences version 20.0 software for Windows (IBM SPSS Corp.; Armonk, NY, USA).

Main Points:

- Both thiol and IMA levels are markers that demonstrate dynamic variability as oxidative stress increases.
- In this study, we investigated the differences of thiol, disulfide, or index values and the angiographic scoring systems and serum IMA levels between the two groups as ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI)/unstable angina pectoris patients.
- We found statistically significantly lower thiol levels and higher IMA levels in the STEMI group in which the affected myocardial area is more and therefore oxidative stress is higher.

Table 1. Demographic characteristics and laboratory findings of the study groups

	STEMI (n=49)	NSTEMI/USAP (n=93)	p
Age, years	59±12.9	61.2±12.6	0.324
Sex (% female)	10 (20.4)	28 (30.1)	0.238
Hypertension (%)	26 (53.1)	51 (54.8)	0.861
Diabetes mellitus (%)	17 (34.7)	37 (39.8)	0.590
Hyperlipidemia (%)	16 (32.7)	34 (36.6)	0.714
COPD (%)	6 (12.2)	7 (7.5)	0.372
PVD (%)	9 (18.4)	14 (15.1)	0.637
Smoking (%)	29 (59.2)	43 (46.2)	0.161
LMCA (%)	3 (6.1)	10 (10.8)	0.543
Number of diseased vessels			
1 (%)	10 (20.4)	26 (28)	0.418
2 (%)	18 (36.7)	33 (35.5)	0.883
3 (%)	21 (42.9)	34 (36.6)	0.475
PCI (%)	49	90 (96.8)	0,758
Glucose (mg/dL)	145±78	136±63	0.437
Creatinine (mg/dL)	0.9±0.3	1±0.4	0.137
eGFR	77±15	73±18	0.135
T. Cholesterol (mg/dL)	193±37	199±50	0.464
HDL-C (mg/dL)	43±10	46±25	0.302
LDL-C (mg/dL)	134±36	134±47	0.957
Triglyceride (mg/dL)	140±77	178±131	0.068
CRP (mg/dL)	14.7±29.8	16.9±31.1	0.685
Leukocyte count (K/uL)	11.6±3.7	11.4±6.4	0.906
Hemoglobin (g/dL)	14.1±1.6	13.6±1.9	0.154
Platelet count (K/μL)	245±60	244±65	0.896
Albumin (g/dL)	3.9±0.5	4±0.4	0.550
C-reactive protein/ albumin ratio	3.7 ± 7.4	4.4 ± 8.6	0.605
Peak CK-MB (U/L)	168±170	38±47	<0.001
Peak troponin I (pg/mL)	33157±19539	7163±11788	<0.001
LVEF (%)	48.4±7.1	53.2±8.6	0.001
Gensini	56±25	43±32	0.010
Syntax score	17±6	16±10	0.431
Syntax II score- CABG	22±12	23±12	0.529
Syntax II score- PCI	29±11	28±13	0,144

COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; T. Cholesterol: total cholesterol; HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, LVEF: left ventricular ejection fraction; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; LMCA: left main coronary artery

Table 2. Thiol/disulfide homeostasis and IMA levels of the study groups

	STEMI (n=49)	NSTEMI/USAP (n=93)	p
Native thiol (μmol/L)	331±64	366±51	0.001
Total thiol (μmol/L)	372±67	404±53	0.003
Disulfide (μmol/L)	20.4±6.5	22.8±8.3	0.112
Index I (disulfide/total thiol) (%)	6.4±2.4	5.8±2.5	0.184
Index II (disulfide/native thiol) (%)	5.6±1.8	5.1±1.9	0.148
Index III (native thiol/total thiol) (%)	88.8±3.6	89.7±3.8	0.143
IMA (absorbance units)	0.59±0.12	0.46±0.23	<0.001

IMA: ischemia-modified albumin.

RESULTS

The demographic features of both groups (group 1: STEMI; group 2: NSTEMI/USAP) are presented in Table 1. Age was similar between the groups (59±12.9 vs 61.2±12.6, p=0.32). The numbers of patients with HT, DM, and HL were higher in group 2, and the numbers of patients with peripheral artery disease, left main coronary artery, and smokers were higher in group 1. CK-MB and troponin I levels were higher in the STEMI group as expected. EF was significantly lower in the STEMI group. When the angiographic scoring systems were examined, only the Gensini score differed between the groups. The mean Gensini score was 56±25 in group 1 and 43±32 in group 2 (p<0.05). No significant difference was found between the groups in terms of Syntax and SS II scores calculated by adding clinical factors. In the STEMI group, PCI was performed in all the patients. In the STEMI/USAP group, two patients underwent CABG and one patient received an intense medical follow-up. Except for three patients, all the patients successfully underwent PCI.

Disulfide levels were similar between the two groups. Native and total thiol levels were statistically significantly lower in group 1 (Table 2, Figures 1, 2). In groups 1 and 2, the mean native thiol levels were 331.62 and 366.57 μmol/L (p<0.05) and the mean total thiol levels were 372.47 and 404.61 μmol/L, respectively (p<0.05). Among the index values defined as index 1 (disulfide/thiol), index 2 (disulfide/native thiol), and index 3 (native thiol/total thiol), the index 1 and 2 values were higher in group 1, although the differences did not reach statistical significance. The IMA level was significantly higher in group 1 (Table 2, Figure 3). The mean IMA level was 0.59±0.12 ABSU in group 1 and 0.46±0.23 ABSU in group 2 (p<0.05). The results of the correlation analysis are presented in Table 3. The IMA level weakly positively correlated with peak troponin I (r=0.185, p<0.05). The native thiol level negatively correlated with peak troponin I (r=-0.247, p<0.05). The total thiol level negatively correlated with peak CK-MB (r=-0.175, p<0.05) and peak troponin I (r=-0.232, p<0.05). The disulfide level positively correlated with LVEF (r=0.200, p<0.05).

Table 3. Correlations of the study parameters with IMA and thiol/disulfide homeostasis

	CAR	IMA	Native Thiol	Total Thiol	Disulfide
	r	r	r	r	r
IMA	-0.085				
Native thiol	-0.152	0.025			
Total thiol	-0.134	-0.067	0.966**		
Disulfide	-0.043	-0.056	0.058	0.299**	
Index I	0.019	-0.028	-0.507**	-0.281**	0.789**
Index II	0.026	-0.032	-0.529**	-0.308**	0.770**
Index III	-0.026	0.032	0.529**	0.308**	-0.770**
Gensini	-0.032	0.085	-0.062	-0.019	-0.134
Syntax I score	-0.006	0.034	0.083	0.116	-0.159
Syntax II score -PCI	0.184*	-0.001	-0.034	0.025	-0.010
LVEF	0.056	-0.098	0.004	-0.037	0.200*
Peak CK-MB	0.203*	0.094	-0.164	-0.175*	-0.145
Peak troponin I	0.018	0.185*	-0.247*	-0.232*	-0.192
Leukocyte	0.022	0.054	-0.071	-0.137	0.043
CRP (mg/dL)	0.994**	-0.098	-0.163	-0.142	-0.038
Creatinine	0.300**	-0.177*	-0.019	-0.024	-0.147
Age	0.214*	-0.058	0.039	0.077	-0.047

PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; CRP: C-reactive protein; CAR: C-reactive protein-to-albumin ratio. *p<0.05, **p<0.001

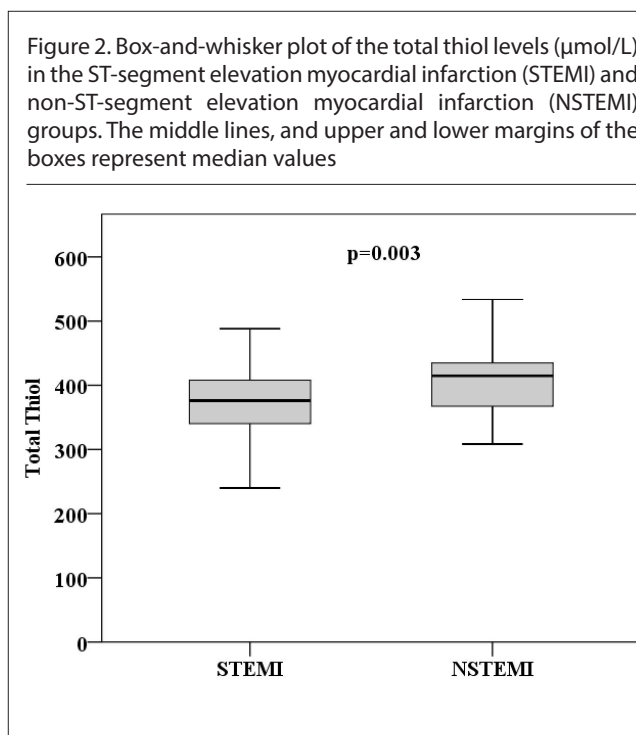
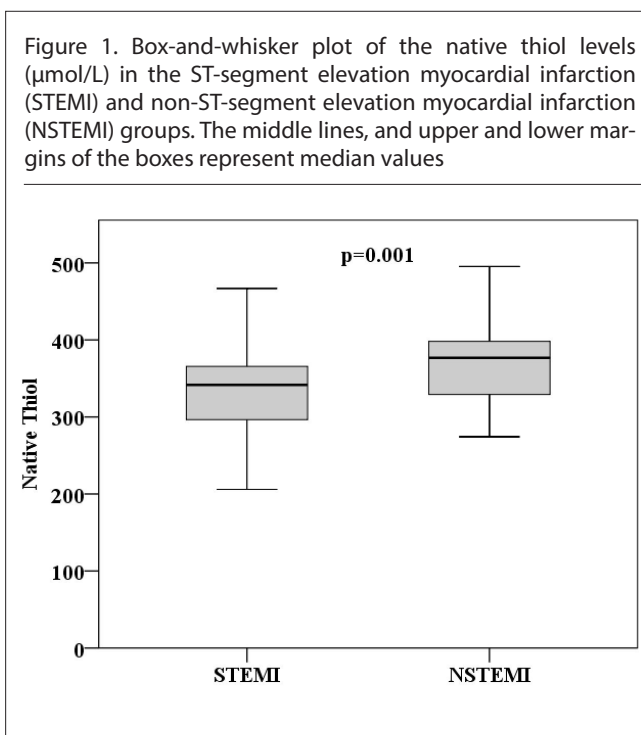
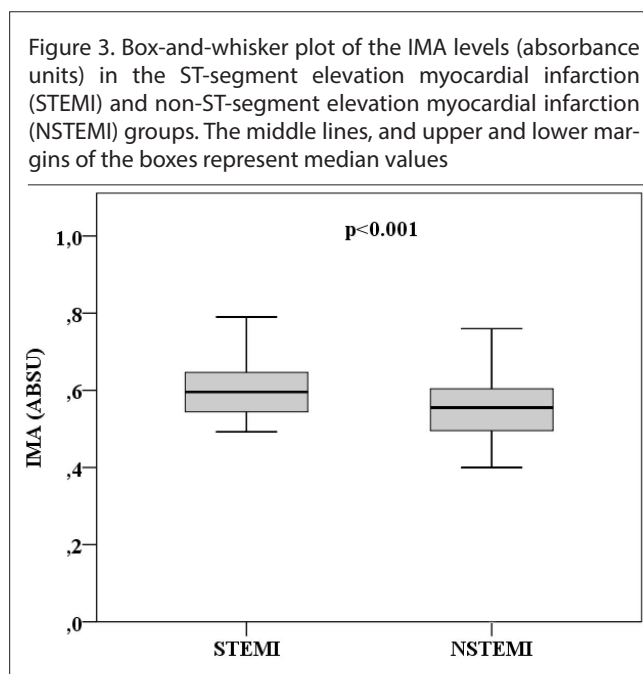


Table 4. Results of the logistic regression analysis between the Gensini score and thiol/disulfide homeostasis and IMA levels of the study groups

	Beta	t	p	Confidence Interval	
				Lower Bound	Upper Bound
Native thiol (µmol/L)	-0.076	-0.732	0.466	-0.143	0.066
Total thiol (µmol/L)	-0.075	-0.701	0.485	-0.139	0.066
Disulfide (µmol/L)	-0.104	-0.996	0.322	-1.119	0.372
IMA (absorbance units)	0.271	2.598	0.011	8.976	67.585

IMA: ischemia-modified albumin



In addition, the C-reactive protein/albumin ratio (CAR) positively correlated with Syntax II score ($r=0.184$, $p<0.05$), peak CK-MB level ($r=0.203$, $p<0.05$), creatinine level ($r=0.300$, $p<0.001$), and age ($r=0.214$, $p<0.05$; Table 3). We found no relationship between the Syntax scores and the IMA and thiol/disulfide levels. Only the Gensini score was related to the IMA level ($p=0.011$, 95% confidence interval=38.280 [8.976–67.585]) in the study group. The results of multivariate logistic regression analysis between the Gensini score and thiol/disulfide and IMA levels in the study groups are shown in Table 4.

DISCUSSION

In our study, disulfide levels were similar between the STEMI and NSTEMI/USAP groups. However, the native and total thiol levels were lower in the STEMI group; thus, thiol/disulfide homeostasis shifted in favor of disulfide, indicating the correlation between increased myocardial damage and disulfide, which is the oxidative form of thiol. In addition, the significantly higher IMA levels in the STEMI group and its significant positive correlation with

peak troponin I show that the serum level increases as the infarcted myocardial area increases.

As an indicator of chronic inflammation, low thiol level is interpreted as a marker of atherosclerosis and CAD as in many systemic diseases (27). In a study by Altıparmak et al. (9), patients were divided into those with and those without CAD. Even CAD patients were classified into those with noncritical and those with critical stenosis according to stenosis severity. The lowest levels of native thiol, total thiol, and disulfide were found in the CAD group with critical stenosis. Disulfide levels were similar between the noncritical and critical stenosis groups, with significantly lower native and total thiol levels in the critical stenosis group. A negative correlation was found between the Gensini score, which is a marker of the prevalence of CAD and an anatomical score, and thiol level, and native thiol was found to be an independent predictor of the Gensini score. In the first of the two separate studies by Kuntı et al. in patients with ACS, patients with MI were compared with the control groups. They found that the thiol levels were significantly lower and thiol/disulfide homeostasis shifted in favor of disulfide in the MI group (10). In a study that included 290 patients (11), this time, only patients with NSTEMI were included and divided into two groups, those with low (<23) and those with high (≥ 23) Syntax scores. The thiol/disulfide ratio was significantly lower in the high Syntax group, and a significant negative correlation was found between the thiol/disulfide and Syntax scores. These results indicate that the disulfide level was linearly increased with the prevalence and CAD severity. In our study, a lack of correlation between the angiographic scoring systems and the thiol and IMA levels might have resulted from the small number of patients. We included only patients with ACS in our study. In conclusion, we observed that thiol levels were significantly decreased with the increase in myocardial area. However, we could not find a correlation between the thiol, disulfide, or index values and the angiographic scoring systems. We thought that the presence of clinical factors such as age, EF, COPD, or PVD, which are used to calculate the SS II score, may have affected the thiol levels, but the SS II values were similar between the two groups. In a 6-month follow-up study, Akkuş et al. investigated the association of thiol levels with major cardiovascular events (MACEs) in patients with STEMI (28) by comparing 241 patients with STEMI patients with controls

with normal coronary arteries. The authors found that the native and total thiol levels correlated with N-terminal brain natriuretic peptide (NT-proBNP) level, Cr level, and contrast nephropathy, and the disulfide levels correlated with the NT-proBNP level. At a 6-month follow-up, they found that besides EF, low-density lipoprotein cholesterol, and serum albumin levels, the native and total thiol levels were also involved among the factors contributing to the development of MACEs and long-term morbidity. Therefore, according to the results of the study, thiol levels can provide information to clinicians about the prognosis of patients with MI.

Normally, the IMA level increases with the modification of albumin level as a result of ischemia and hypoxia occurring when coronary blood flow decreases, even before the levels of the cardiac markers increase with elevated blood levels (CK, CK-MB, lactate dehydrogenase, cardiac troponin I, and cardiac troponin T [cTnT], and myoglobin) in myocardial necrosis (14, 29). IMA is an efficient and inexpensive test with high sensitivity for the early diagnosis of ACS, which has been approved by the Food and Drug Administration in 2003. The IMA level increases within minutes immediately after the onset of ischemia, remaining high for 6 to 12 hours and returning to normal within 24 hours (16). In a diagnostic study by Sinha et al. for ACS, the sensitivity of IMA level was shown to increase to 95% when the marker was used together with electrocardiography and cTnT (17). In addition, in a study by Kazanis et al, IMA levels after exercise were demonstrated to be useful to detect ischemia not only in ACS but also in stable CAD. IMA levels were higher and total antioxidant status was lower in patients with stable CAD than in healthy controls (30). Again, in a study by Manneewong et al. about ischemia and infarction, serum IMA levels were significantly higher in patients with NSTEMI (31). It can be said that ROS leading to protein oxidation is less severe in association with minor myocardial damage rather than major myocardial necrosis in patients with NSTEMI. On the basis of this opinion, we tested the correlation between the affected infarction area and IMA with a categorization of the patients into STEMI and NSTEMI/USAP groups. We observed that EF was significantly lower and peak troponin I levels were significantly higher; thus, the infarction area was larger, and IMA levels were higher in the STEMI group. Moreover, we found a significant positive correlation between the IMA and peak troponin I levels. The results suggest that like thiol or serum albumin level, IMA level may be a predictive factor of MACEs and prognosis in patients with MI. However, we believe that further long-term follow-up studies are needed to confirm these results.

Another remarkable result of the study is the positive correlation of CAR with SS II score. CRP level is known to indicate endothelial dysfunction, and hypoalbuminemia is associated with new MI development and increased mortality in patients with ACS (32). On the basis of the same rationale, Çınar et al. recently published a study in which patients with STEMI were examined for CAR values. They showed that CAR is an independent predictor of all-cause mortality and associated with increased myocardial damage. They observed that increased CAR was significantly associated with advanced heart failure during in-hospital stay and long-term follow-up, and myocardial reinfarction (33). In our study, we included all patients with ACS (STEMI and NSTEMI/

USAP) and observed no significant difference in CAR between the two groups. We found no significant relationship between CAR with IMA, thiol/disulfide homeostasis, and LVEF. Only a positive correlation was found between CAR and SS II score. SS II is known to be superior to the Syntax score in revascularization decision because it is calculated together with the clinical features and coronary anatomical score of patients. This relationship seems important in terms of providing a preliminary idea to the interventional cardiologist simply by laboratory examination before scoring. However, these results should be supported by larger studies.

CONCLUSION

Both thiol and IMA levels are markers that show dynamic variability as oxidative stress increases. The statistically significantly lower thiol levels and higher IMA levels in the STEMI group than in the NSTEMI group show that oxidative stress was increased and the antioxidative stress capacity was decreased with the reduced thiol levels in the STEMI group. Both blood tests are studied with a spectrophotometric method, which is a relatively inexpensive and rapid technique. As these tests are likely to guide clinicians, the present study will contribute to the literature.

Study Limitations

The lack of a correlation between the angiographic scores and the thiol, disulfide, and IMA levels may be attributed to the small number of patients included in the study. One of the other limitations of this study is the lack of a long-term follow-up of the patients because this study was aimed at investigating the association between blood test results and the affected myocardium. We believe that further long-term follow-up studies are needed to investigate the associations between clinical course and prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Biruni University.

Informed Consent: The patients were informed before the study and written consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.E., F.H.; Design - E.E., F.H. E.Y.; Supervision - M.D., M.C.; Resources - E.E., H.U., S.A. ; Materials - F.H., S.N., Ö.E.; Data Collection and/or Processing - E.E., S.A., E.Y.; Analysis and/or Interpretation - E.E., M.D., M.C.; Literature Search - F.H., E.Y., S.N., Ö.E.; Writing Manuscript -E.E., F.H.; Critical Review - H.U., M.D., M.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

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