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A New Biomarker in The Distinction Between Stable Coronary Artery Disease and Acute Coronary Syndrome: Thiols

Stabil Koroner Arter Hastalığı ile Akut Koroner Sendrom Arasındaki Ayrımda Yeni Bir Biyobelirteç: Tiyoller

Gökhan Ergün[1], Şaban Keleşoğlu[2], Kemal Abid Tekin[1], Bekir Çalapkorur[1], Fatih Balcı[3], Özcan Erel[4], Salim Neşelioğlu[4], Deniz Elcik[2]

[1] University of Health Sciences, Kayseri City Training and Research Hospital, Department of Cardiology, Kayseri, Turkey
[2] Erciyes University, School of Medicine, Department of Cardiology, Kayseri, Turkey
[3] University of Health Sciences, Kayseri City Training and Research Hospital, Department of Anesthesiology and Intensive Care Medicine, Kayseri, Turkey
[4] Yıldırım Beyazıt University, Faculty of Medicine, Department of Biochemistry, Ankara, Turkey

Abstract

Aims: Thiols are important elements for oxidation reactions and under oxidative stress. The aim of this study was to determine thiole levels, an antioxidative marker in coronary artery disease patients with stable and acute coronary syndrome.

Material and Method: 210 of the patients included in the study were diagnosed with acute coronary syndrome (ACS), 205 consisted of patients with stable angina pectoris (SAP). Thiol groups levels and thiol/disulphide homeostasis was measured by spectrophotometrically.

Results: Native thiol (332.03±59.84 to 404.71±67.64, p<0001 and total thiol levels (367.07±64.62 to 454.28±78.49, p<0001), disulfide (17.52±8.56 to 24.79±11.17, p<0001, native thiol/disulfide (5.3±2.6 to 6.1±2.5, p<005) and total thiol /disulfide (4.77±2.08 to 5.36±2, p<003) ratios were decreased in the ACS groups compared to the SAP groups

Conclusions: Thiol levels and thiol / disulfide ratios can be used as markers to evaluate ACS.

Keywords: Thiol, acute coronary syndrome, stable angina pectoris

Öz

Amaç: Tiyoller, oksidasyon reaksiyonları ve oksidatif stres durumlarında önemli elementlerdendir. Bu çalışmanın amacı, stabil koroner arter hastalığı hastalarında ve akut koroner sendromlu (AKS) hastalarda bir antioksidan belirteç olan tiyol düzeylerini belirlemektir.

Gereç ve Yöntem: Çalışmaya 210'u AKS, 205'i ise stabil angina pektoris (SAP) tanısı alan hasta dahil edildi. Tiyol gruplarının seviyeleri ve tiyol/disülfid homeostazı spektrofotometrik olarak ölçüldü.

Bulgular: SAP gruplarına kıyasla AKS gruplarında nativ tiyol düzeyleri (332,03±59,84' e karşı 404,71±67,64, p<0001, toplam tiyol düzeyleri (367,07±64,62' e karşı 454,28±78,49, p<0001), disulfid (17,52±8,56' e karşı 24,79±11,17, p<0001, nativ tiyol/disulfid (5,3±2,6' e karşı 6,1±2,5, p<005) ve toplam tiyol/disulfid (4,77±2,08' e karşı 5,36±2, p<003) oranları azalmış olarak tespit edildi.

Sonuç: Tiyol düzeyleri ve tiyol/disülfid oranları AKS' yi değerlendirmede belirteç olarak kullanılabilir.

Anahtar Kelimeler: Akut koroner sendrom, tiyol, stabil angina pectoris

Corresponding *(İletişim)*: Gökhan Ergün, University of Health Sciences, Kayseri City Training and Research Hospital, Department of Cardiology, Kayseri, Turkey,
E-mail *(E-posta)*: 2015.drergun@gmail.com
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INTRODUCTION

Despite all the developments in diagnosis and treatment, atherosclerotic heart diseases still account for more than 1/3 of the total deaths worldwide.[1] Several of the pathological mechanisms of atherosclerosis, in order of occurrence, such as endothelial dysfunction, lipid penetration and accumulation into the vascular intima, exaggerated adaptive immune responses, vascular smooth muscle cell proliferation, and extracellular matrix remodeling.[2] On the other hand, some studies have shown that oxidative stress plays a role in atherosclerosis.[3-6] When the oxidant stress occurs, it causes endothelial dysfunction; activates an inflammatory response, immune reaction and thrombus formation, oxidized lipids are formed; and initiates sequential vascular events.[7,8]

Thiol groups are an antioxidant cascade that plays a vital role in the elimination of reactive oxygen species.[9,10] The components of antioxidants that provide homeostasis in this group are total thiol, natural thiol, disulfide and derived from them, disulfide / natural thiol, natural thiol/total thiol and disulfide/total thiol ratios. Thiols are an organic compound containing a sulfhydryl (-SH) group, which reacts with reactive oxidant molecules and neutralizes them. Their primary function is to prevent the formation of any oxidative stress state in cells and organisms.[10,11] When thiols cause an antioxidation reaction, it causes the formation of reversible disulfide bonds. When the oxidation reaction is compensated, the disulfide bonds formed can be reduced back to thiol groups. In other words, the thiol/disulfide balance is dynamic and can be maintained through this cycle. The evaluation of this balance gives information about oxidation-antioxidation structure in plasma. Adverse changes in the thiol- disulfide balance can cause disruptions in the normal function and structure of organs and eventually cause diseases such as diabetes, malignancy and atherosclerotic heart diseases.[12,14]

Few studies have observed the relationship between coronary artery disease (CAD) and thiol levels. The present study aimed to determine thiol levels, an antioxidative marker in CAD patients with stable angina pectoris (SAP) and acute coronary syndrome (ACS), and to compare these parameters between these groups.

MATERIAL AND METHOD

A total of 415 patients were included in this study. While 210 of these patients had been diagnosed with ACS, 205 had been diagnosed with SAP. In the ACS group, 75 were ST-segment elevation myocardial infarction (STEMI), 87 were non-STEMI, and 48 were unstable angina pectoris (UAP). Medical history, including cardiovascular risk factors and medications, was recorded on all participants. Routine physical examinations of all patients were performed.

During hospitalization, SAP and the occurrence of ACS (STEMI), non-STEMI, UAP), and SAP are recognized by standard criteria.[15,16] Patients admitted with ACS performed coronary angiography for invasive emergency strategy and continued with a percutaneous coronary intervention (PCI) where necessary. In the other patient group, it was generally accepted for coronary angiography to be performed, and PCI continued when necessary with the intervention and treatment strategy determined by clinicians. Selective coronary angiography (CAG) was performed using the Judkins technique with 6 or 7 French (F) catheters with a right or left femoral approach. Iopromide (Ultravist-370®) or Iohexol (Omnipaque® 350 mg / mL) was used as an opaque agent. In all patients, coronary arteries were visualized with cranial and caudal tilt in the left and right oblique planes. The patients with a PCI procedure were continued with a 6 or 7 F guiding catheter. The stent was implanted, and the length of the lesion calculated by at least two invasive cardiologists.

On admission to the hospital (coronary intensive care or coronary angiography service), venous blood samples were obtained, which measure baseline blood variables (such as comprehensive metabolic panel and complete blood count) and thiol levels. The samples for thiols were centrifuged at 1500g for 10 min. The plasma was stored at -80°C and all samples were processed simultaneously. Thiol group levels and thiol/disulfide homeostasis was measured as defined by Erel et al (17). Serum natural thiol and total thiol levels were determined spectrophotometrically. First, serum natural thiol levels were measured after the reaction without any treatment with 5, 5'-dithiobis-2-nitrobenzoic acid (DTNB). Second, to measure total thiol levels, dynamic disulfide bonds in serum samples were reduced using sodium borohydride (NaBH4) to form free functional thiol groups. Then, formaldehyde was used to remove unused NaBH4 completely, and total thiol groups, including both reduced and natural ones, were measured following the reaction with DTNB. Since the reduction of a disulfide bond produces two separate thiol groups, the number of dynamic disulfide bonds was calculated by determining half of the difference between total thiol and natural thiol.

During hospitalization, medical treatment regimens were applied to all patients according to the current guidelines of the European Society of Cardiology.[16,18,19]

Exclusion criteria were evaluated as follows: age<18 years, continuing infection, inflammatory disorders, congenital heart disease, severe valvular heart disease, untreated cancer, pregnancy, organ failures and the taking of supplemental vitamins.

Before study inclusion, all patients gave their written informed consent. The research protocol of the present investigation was approved by the local research ethics committee and complies with the Declaration of Helsinki (Kayseri City Hospital, Clinical research ethics committee; 03/2020-20)

Statistical Analyses

All analyses were performed using SPSS V 21.0 for Windows (version 21.0; SPSS, Chicago, Illinois). All data are presented as mean±standard deviation unless otherwise stated. The Kolmogorov-Smirnov test was used to analyze the distribution pattern. A comparison of parametric values between the two groups was performed employing independent samples t-test. A comparison of nonparametric values between the two groups was performed by the Mann-Whitney U test. Continuous variable distribution among the groups was done by One Way Anova. Variability between groups was performed by the LSD test. Categorical variables were compared with the chi-square test. Receiver operating characteristic curve (ROC) analysis was used to determine native thiol, total thiol, disulfide and diagnostic value of ACS. P-value<0.05 was accepted as significant.

RESULTS

A total of 415 patients were included in the study (mean age 62.7±10.61). While 210 of the patients included in the study created ACS (STEMI, non-STEMI, UAP), 205 of them constituted stable CAD. Baseline characteristics between ACS and stable CAD are given in **Table 1**. Also, the presence of hypertension, diabetes mellitus, dyslipidemia, and smoking were similar in all groups (**Table 1**).

Table 1: Basal characteristic, biochemical and hematological parameters between groups.

Variables	Acute Coronary Syndrome (n=210)	Stable Angina Pectoris (n= 205)	P value
Age	63.5±10.9	62 ±10.8	.172
Hypertension, n (%)	87	82	.754
Diabetes mellitus, n	58	50	.824
Hyperlipidemia, n	79	81	.814
Smoking, n	105	102	.911
Left ventricular ejection fraction	47.1±9.6	50±10.24	.0001*
Glucose	160.4±88.6	128.8±55.7	.0001*
Blood urea nitrogen	19.4±8.38	16.3±6.53	.0001*
Glomerular filtration rate	89±23.79	91.8±25.7	.320
Creatine	1.8±8,9	1.4±6.6	.588
Aspartate aminotransferase	36.3±29.6	24.3±19.2	.0001*
Alanine aminotransferase	27.6±12.3	20.3±14.1	.001*
Total cholesterol	182.1±41.2	200.3±46.6	.0001*
Triglyceride	158.9±81.8	161.2±73.2	.165
High-density lipoprotein-cholesterol	41.4±11.8	40.4±16.4	.443
low density lipoprotein- cholesterol	111.2±35	116.4±40.2	.183
Sodium	138.4±6.34	137.6±10.8	.315
Potassium	4.5±2.4	5.6±10.5	.131
Hemoglobin A1c	8.8±2.7	7.7±1.7	.018*
Uric acid	6,6±5.7	5.4±1.5	.408
White blood counts	12.5±3.6	8.6 ±3.8	.0001*
Hemoglobin	14.3±1.8	14.5±1.8	.254
Platelets	252.4±78.6	263.2±76.6	.165

Data are expressed as mean ± standard deviation for normally distributed data. *statistically significant (p<0.05)

Laboratory analyses revealed no significant difference between the groups in terms of biochemical parameters such as LDL cholesterol, HDL cholesterol, triglyceride levels, urea and creatinine levels (p>0.05) (**Table 1**). However, since one of the groups ACS, AST, ALT, and glucose values were significantly different in the ACS group (p<0.001, p=0.001 and p<0.001, respectively) (**Table 1**).

When the hematological parameters are examined between the two groups, there is no significant difference between hemoglobin and platelet values (p>0.05). In contrast, a significant difference was found in the white blood cell count (p<0.001) (**Table 1**). Because the patient groups had ACS, a significant difference was detected in the left ventricular ejection fraction.

When the native thiol and total thiol droplets were examined between the two groups, a statistically significant difference was found (p<0.001) (**Table 2**). The disulfide /native thiol and disulfide /total thiol ratios decreased in the ACS group compared with SAP. In subgroup analysis, both native thiol, total thiol, disulfide value and their rates were low in all ACS groups. Interestingly, this change was not significant in the subgroup analysis. However, there was no difference between the STEMI groups and non-STEMI groups or between the STEMI groups and the UAP groups or between the non-STEMI groups and UAP. Still, a significant difference was observed between all subgroups and SAP group. (**Table 3**) (**Figure 1**).

Table 2: Relationship between thiol and disulfide between groups

Variables	Acute Coronary Syndrome (n=210)	Stable Angina Pectoris (n= 205)	P value
Native thiol	332.03±59.84	404.71±67.64	.0001*
Total thiol	367.07±64,62	454.28±78.49	.0001*
Disulfide	17.52±8.56	24.79±11.17	.0001*
Native thiol / disulfide	5.3±2.6	6.1±2.5	.005*
Total thiol / disulfide	4.77±2.08	5.36±2	.003*

Data are expressed as mean ± standard deviation for normally distributed data. *statistically significant (p<0.05)

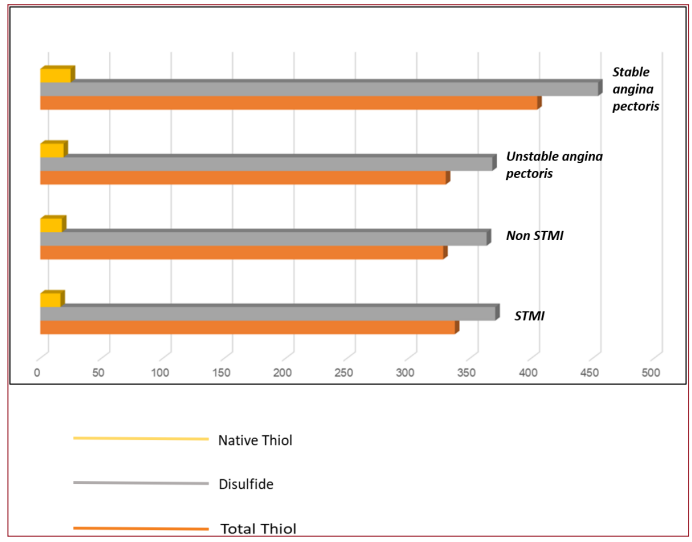

Figure 1: Analysis of thiol and disulfide levels relation of all subgroups

Table 3: Anova test data of thiol and disulfide relation of all subgroups

Variables	STEMI (n=75)	NonSTEMI (n=96)	Unstable angina pectoris (n=48)	Stable Angina pectoris (n=246)	Control (n=72)	P value
Native thiol	260.86±37.49	330.66±11.65	360.31±5.14	413.52±30.62	514.46±33.26	>0001*
Total thiol	289.19±40.60	366.91±13.92	400.09±5.51	461.06±34.25	584.64±41.43	>0001*
Disulfide	16.64±7.49	20.74±2.5	20.25±9.53	22.01±11.79	33.16±11.51	>0001*
Native thiol / disulfide	0.058±0.027	0.055±0.07	0.0505±0.023	0.046±0.023	0.057±0.02	,024*
Total thiol / disulfide	0.065±0.03	0.061±0.78	0.056±0.26	0.051±0.026	0.065±0.022	,022*

Data are expressed as mean ± standard deviation for normally distributed data. STEMI: ST elevated myocardial infarctions, *statistically significant (p<0.05)

Other interesting data of the study are the receiver operating characteristic curve (ROC) analysis results. In the ROC analysis, it was determined that native thiol, total thiol, and disulfide ratios were quite sensitive and specific in finding stable CAD. This analysis is stable CAD with 63% sensitivity and 66% specificity for disulfide 17.5 shear value with 73% sensitivity and 70% specificity for 361.3 shear value of natural thiol, with 71% sensitivity and 70% specificity, showed that he predicted arterial disease (p<0.001 in three values) (**Figure 2**).

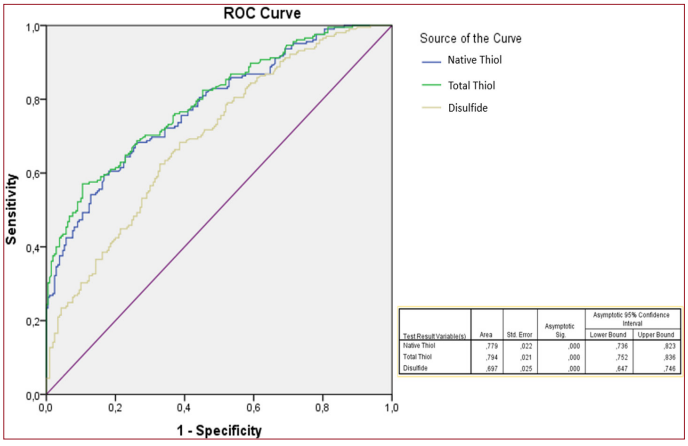

Figure 2: Receiver–operating characteristic analysis and curve for predicting stable coronary disease.

DISCUSSION

Our study is the first to investigate the relationship between thiol levels and disulfide/thiol ratio among all subgroups of ACS patients. We found that native and total thiol levels were significantly decreased in patients with the STEMI, non-STEMI, and UAP patients than the SAP groups. We did not find any significant difference between the ACS subgroups. Also, another interesting finding was shown in the ROC analysis: thiol and disulfide values predict an average of 70% sensitive and 70% specificity in detecting patients with SAP.

Oxidative stress can be described as the disruption of the balance between oxidants and antioxidants in favor of oxidants and causes harmful effects.[20] Oxidants (reactive oxygen species (ROS), which are the products of aerobic cellular metabolism, can occur in the intracellular or extracellular environment.[21-23] Physiologically, to maintain the oxidant-antioxidant balance, it is adapted to the body's antioxidant defense system composed of enzymes such as superoxide dismutase, glutathione peroxidase and catalase, enzyme-free molecules such as albumin, bilirubin and glutathione.[24,25] When oxidants are produced in large quantities or cannot be eliminated by antioxidants, cells cause active ROS to attack and changes occur.[24,26-28] Oxidative stress and inflammation are closely interrelated, and both cause injury to many cells in which they are involved in the endothelium and endothelial dysfunction is the first stage of atherosclerosis.[29-31] In our study, thiol and disulfide values and rates, which are the pre-emptive markers of the antioxidant system, were significantly lower than the stable CAD.

Thiols are sulfur analogs of alcohols and disulfides are structures containing adjacent double sulfur atoms.[13,32] The role of thiol/disulfide balance is vital in antioxidant reactions. Also, thiols, which are among the main components of intracellular and extracellular damage protection mechanisms, are non-enzymatic antioxidants. Plasma thiol groups reduce oxidative damage in diseases in the pathophysiology of inflammatory processes such as CAD, rheumatoid arthritis and diabetes mellitus.[33,34] In our study, low levels of thiol and disulfide in high ACS, especially in patients with stable CAD, may be evidence of the effect of the inflammatory and antioxidant system.

The relationship between atherothrombotic cardiovascular disease and oxidant stress has been demonstrated in several studies. These studies have shown that increased oxidant stress markers predict coronary heart disease and predict patients with coronary artery risk factors such as diabetes, hypertension, smoking, hyperlipidemia and obesity.[7] In the study of Schwedhelm et al., isoprostanes, which are considered as a marker of oxidant stress and are formed by peroxidation of arachidonic acid and are found to be high in patients with CAD and and showed that the risk of this disease increased by 30.8 times in those with the highest level of tertile isoprostane.[35] Shishehbor et al. found that plasma isoprostane levels were significantly higher in CAD with significant coronary artery stenosis.[36] Moreover, in the studies by Shishehbor et al and Guzik and et al., it was found that nitrotyrosine levels and expression of the NAD(P)H oxidase were significantly higher in patients with CAD than in controls.[37,38] Walter et al. found that serum lipid hydroperoxides levels during admission are also an independent indicator of the development of major adverse cardiovascular events.[39] In our study, low levels of thiol and disulfide may have triggered ACS. In other words, it should not be forgotten that it may be the cause, not the result.

The importance of antioxidants for atherothrombotic vascular disease occurs when there is a decrease in the catalytic activity of antioxidant enzymes. Decreased enzyme expression, genetic polymorphism, change in the functional properties of the enzyme, all result in reduced antioxidant capacity.[7] In the Espinola-Klein et al study, in the long-term follow-up of patients with documented atherosclerotic vascular disease, the lowest GPx-1 activity and the highest experience of cardiovascular events were determined. [40] Chen et al. and Dick et al. have shown that less heme oxygenase expression was associated with an increased risk of restenosis in peripheral arterial disease following an intervention. At the same time, successful coronary artery stenting procedures revealed that they were associated with an increased risk of restenosis as well as major adverse coronary and cerebrovascular events.[41,42] Elcik et al suggested that the thiol disulphide volume on admission was independently associated with the development of contrast-induced nephropathy after PCI in patients with ACS. [43] In our study, following these data, it was low in a severe event such as ACS.

In the literature, studies revealing the relationship between plasma thiol levels and thiol/ disulfide ratio and CAD are limited. Altiparmak et al demonstrated that the disulfide/ thiol ratio did not change significantly, but decreased native thiol levels were associated with the presence and severity of CAD.[9] Kundi et al showed that native thiol, total thiol and disulfide levels were lower in acute myocardial infarction (AMI) patients when compared to the controls and mean disulfide/native thiol and mean disulfide/total thiol ratios were higher in patients with AMI patients.[44] In our study, it has been shown that these values are high in patients with stable CAD, in addition to ACS patients. As a result, an antioxidant deficiency is thought to trigger ACS: it can indicate a significant difference between the stable patient and the unstable patient.

In the study published by Morrow et al., oxidant stress marker, myeloperoxidase concentration in patients with myocardial infarction was higher than those with UAP and associated with adverse complications such as non-fatal myocardial infarction or recurrent ACS events within the first 30 days.[45] Kundi et al study showed that the comparison of STEMI and non-STEMI patients did not reveal any differences for thiol, total thiol and disulfide levels or disulfide/ native thiol and disulfide/ total thiol ratio.[44] In our study, similar to Kundi et al. and the opposite of Morrow et al, plasma thiol levels and thiol/disulfide ratio decreased in the STEMI patients. However, there was no difference between the STEMI patients and the non-STEMI patients or any other subgroup of the ACS. Besides, in our study, in contrast previous studies, it was also found that thiol levels and thiol/ disulfide ratio were lower in the UAP patients compared to the stable CAD group. On the other hand, we found that there was no statistically significant difference between the ACS subgroups in thiol levels and thiol/disulfide ratios. It can be assumed that the decrease in serum thiol and disulfide levels is due to the use of reactive free radical and non-radical species to limit their harmful effects and pathophysiological sequences. These results suggest that thiol levels and thiol/ disulfide ratios can be used as markers to evaluate ACS.

Our work had some limitations. Firstly, this was a single-center retrospective study and there was a comparatively small number of patients. Thus, the selected population may not represent the whole aimed cohort. The second limiting factor was the evaluation of thiol levels with only one measurement. We did not evaluate the follow-up period. This is the first study to show these results: new studies with a more significant number of patients are needed to confirm the results obtained.

CONCLUSION

We think that ACS, which is quite difficult to distinguish, may be a new marker in distinguishing UAP from stable CAD. Besides, we have once again demonstrated the antioxidant system effect in ACS pathology in this study.

This is the first study to show these results: new studies with a more significant number of patients are needed to confirm the results obtained.

ETHICAL DECLARATIONS

Ethics Committee Approval: Kayseri City Hospital, Clinical research ethics committee; 03/2020-20

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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