■ Original Article

The association of thiol/disulphide homeostasis with 6-month mortality in patients with acute St-elevation myocardial infarction

Akut St-elevasyonlu miyokart infarktüsü hastalarinda 6 aylik mortalite ve thiol / disulfid ilişkisi

Mustafa CELIK[1]* ⓘ, Erdoğan SOKMEN[1] ⓘ, Murat ERER[1] ⓘ, Serkan SIVRI[1] ⓘ, Alp YILDIRIM[1] ⓘ, Yalçın BODUROGLU[1] ⓘ, Kenan GUCLU[2] ⓘ, Sinan Cemgil OZBEK[1] ⓘ

[1]Department of Cardiology, Ahi Evran University Training and Research Hospital, Kirsehir, TURKEY
[2]Department of Biochemistry, Ahi Evran University Training and Research Hospital, Kirsehir, TURKEY

ABSTRACT

Aim: Acute ST-elevation myocardial infarction (STMI) is significant determinant of mortality and long-term mortality rates has not changed significantly over the last two decades. Thiols are an important anti-oxidant mechanism in the body, and excessive reactive oxygen species oxidize the thiol into their disulphide forms. Hence, higher level of disulphide is regarded as an indicator of oxidative stress. In the present paper, we sought to investigate any probable relationship between thiol/disulphide homeostasis and 6-month all-cause mortality among STMI survivors.

Material and Methods: 238 consecutive patients with STMI undergoing percutaneous coronary intervension were included. Blood samples for thiol/disulphide homeostasis were drawn on admission. Syntax I and II scores were calculated using the cineangiographic views and relevant patient demographics.

Results: 6-month mortality occurred in 25 patients (mortality group), while 213 patients remained alive (non-mortality group). Total thiol, native thiol, disulphide, disulphide/total thiol, disulphide/native thiol and native thiol/total thiol were not different between the mortality and non-mortality groups (p>0.05). Syntax I and II scores were significantly greater in mortality group (26.11±8.06 vs 19.129.80, p=0.029 for Syntax I; 50.1314.59 vs 30.639.79, p<0.001 for Syntax II).

Conclusion: Syntax II score, glomerular filtration rate (GFR) and white blood cell count (WBC) were found to predict 6-month mortality.

Keywords: thiol disulfide; acute myocardial infarction; mortality

ÖZ

Amaç: Akut ST yükselmeli miyokard infarktüsü (STMI) mortalitenin önemli bir belirleyicisidir ve uzun dönem ölüm oranları son yirmi yılda önemli ölçüde değişmemiştir. Tiyoller vücutta önemli bir antioksidan mekanizmadır ve aşırı reaktif oksijen türleri tiyolü disülfür formlarına okside eder. Bu nedenle daha yüksek seviyedeki disülfid oksidatif stresin bir göstergesi olarak kabul edilir. Bu yazıda STMI sağ kalanları arasında tiyol / disülfid homeostazı ve 6 aylık tüm nedenlere bağlı ölüm arasındaki olası ilişkiyi araştırmaya çalıştık.

Gereç ve Yöntemler: Çalışmaya perkütan koroner girişim uygulanan STMI' li 238 hasta dahil edildi. Giriş sırasındaki tiyol / disülfit homeostazı için kan örnekleri alındı. Syntax I ve II skorları sineanjiyografik görüntüler ve ilgili hasta demografik özellikleri kullanılarak hesaplandı.

Bulgular: 25 hastada (mortalite grubu) 6 aylık takibinde mortalite izlendi, 213 hastada mortalite izlenmedi (mortalite dışı grup) . Total tiyol, nativ tiyol, disülfid, disülfid / toplam tiyol, disülfid / nativ tiyol ve nativ tiyol / toplam tiyol, mortalite ve mortalite dışı gruplar arasında farklı değildi (p> 0.05). Syntax I ve II skorları mortalite grubunda anlamlı olarak daha yüksekti (26.11 ± 8.06 - 19.12 ± 9.80, Syntax I için p = 0.029; Syntax II için 50.13 ± 14.59 ve 30.63 ± 9.79, p <0.001).

Sonuç: Syntax II skoru, glomerüler filtrasyon hızı (GFR) ve beyaz kan hücre sayımının (WBC) 6 aylık mortaliteyi öngördüğü bulundu.

Anahtar kelimeler: thiol disulfid; akut miyorkard infarktüsü; mortalite

Introduction

For many years, acute myocardial infarction (AMI) has proved to be a significant determinant of both the morbidity and mortality worldwide, despite advances in interventional cardiology and medical therapy. Although a prominent amelioration in the 30-day mortality rates was achieved in AMI, long-term mortality rates however did not change significantly over the last two decades [1]. Acute ST-elevation myocardial infarction (STMI) is one of the entities comprising the term "AMI", and constitutes nearly one third of the patient population worldwide who admit to the hospital with an AMI [2,3]. Accordingly, new measures and predictors are warranted in order for the physicians to anticipate better the long-term mortality rates among the survivors of an acute STMI, and provide a closer-follow up for them.

Oxidative stress occurs when the generation of reactive oxygen species exceeds the dealing capability of bodily anti-oxidant defense mechanisms [4]. Oxidative stress and AMI are not mutually exclusive. In this regard, oxidative stress was previously proposed as a major contributor to both the development and progression of vascular atherosclerosis [5]. On the other hand, the ischemic state incited by an acute STMI also generates another milieu of oxidative stress which in turn gives rise to a further impairment in the antioxidant defense mechanisms.

Thiols are sulfhydryl (-SH) containing organic molecules, in which the sulfhydryl is bound to a carbon atom [6]. Moreover, albumin and protein thiols comprise the major source of total thiol mass in the plasma [6]. Thiols serve as a potent anti-oxidant mechanism in the body. Excessive reactive oxygen species can readily oxidize the thiol groups to transform them into the disulphide forms. Thereby, emergence of higher levels of disulphide forms is regarded as a robust indicator of exposure to oxidative stress [7]. Additionally, this process is reversible, and any tempering in the magnitude of the oxidative stress is likely to initiate the convert the disulphide forms back into their former thiol forms, thus keeping a stable thiol/disulphide homeostasis [8].

Considering the above-mentioned premises, we sought in the present study to investigate any probable relationship between thiol/disulphide homeostasis and 6-month all-cause mortality among the survivors of acute STMI.

Materials and Methods

Study Population

Our prospective study included a total of 238 consecutive patients (64 female and 174 male) who presented to our hospital with the diagnosis of acute STMI and underwent PCI between January 2018 and October 2018. Acute STMI was defined as the presence of the pertinent criteria as follows: detection of rise and/or fall of cardiac troponins with at least

one value above the 99th percentile of the upper reference limit and with at least one of the following features such as ischemia-related symptoms; new or presumably new ST segment elevation in ≥ 2 contiguous leads with the cutoff point of ≥ 0.2 mV in the anterior leads or new left bundle branch block; development of pathological Q waves in the electrocardiogram; imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality; and identification of an intracoronary thrombus by angiography [9].

The exclusion criteria for our study were set as follows: the patients with a history of a recent myocardial infarction; those who had received any thrombolytic agent as a pretreatment; those with active infection or chronic inflammatory disease; those with severe hepatic, renal, hematological disease; and, those with any history of neoplasm or rheumatologic disease.

All the study participants underwent a scrutiny including a detailed medical history and a thorough physical examination and recording such baseline demographic features as age, sex, hypertension, chronic obstructive pulmonary disease, peripheral arterial disease, chronic obstructive pulmonary disease, smoking habit, diabetes mellitus, and coronary arterial disease.

Either a written or an oral-witnessed informed consent was obtained from all of the participating patients provided at the emergency service. Our study was performed by complying with the principals by the Declaration of Helsinki and was approved by the local ethics committee.

Echocardiography

Transthoracic echocardiographic evalation of the enrolled patients were performed using Vivid S5 (GE Vingmed Ultrasound AS, Horten, Norway). Left ventricular ejection fraction was calculated using the modified Simpson's rule. All the conventional echocardiographic examination were performed according to the standards of the American Society of Echocardiography [10].

Coronary Angiography and Percutaneous Coronary Intervention

All patients were treated by complying with the recommendations of the STMI guideline [11]. Once the written informed consent for cardiac catheterization was obtained, an emergency coronary angiography was performed in all patients using the standard techniques. Glycoprotein IIb/IIIa inhibitor (tirofiban) was administered to the patients in the catheterization laboratory at the operator's discretion. Decision regarding the implementation of percutaneous coronary intervention (PCI), coronary artery bypass graft surgery or medical treatment was given by a heart team comprising two cardiologist and one cardiovascular surgeon. All PCIs performed in eligible patients were performed using the standard clinical practice and choice between the alternatives of drug-eluting stent or bare metal stent was at the operator's discretion. Stenting of infarct-related artery was successfully fulfilled in all patients.

Blood Samples and Laboratory Analysis

Blood samples were obtained through venipuncture on admission to the emergency department. The collected blood samples were centrifuged at 1500 g for 10 min to separate the serum. Serum was stored at −80 °C until analysis of thiol/disulfide homeostasis tests.

Routine serum biochemical parameters were measured by using an automated clinical chemistry analyzer (Roche Hitachi Cobas c8000 autoanalyzer, Roche Diagnostic Corp., Mannheim, Germany).

Thiol/disulfide homeostasis test levels were measured using a newly developed, fully-automated and spectrophotometric method by Erel and Neşelioğlu [12]. After determining native and total thiols, the concentration of disulfide was determined using the formula: Disulfide = (total thiol − native thiol) / 2

The ratios of disulfide/total thiol (%), disulfide/native thiol (%) and native thiol/total thiol (%) were calculated using the concentrations of disulfide, native thiol and total thiol, which were previously determined.

Calculation of the SYNTAX I and SYNTAX II Scores

Assessment of the cineangiographic views was performed using Axiom (Siemens Medical Solution, Erlangen, Germany) workstation by two experienced cardiologist blinded to the study data. Each lesion with a diameter stenosis ≥50% in coronary vessels ≥1.5 mm in diameter was scored using the online SYNTAX score calculator (http://www.syntaxscore.com). If the cardiologists conflict about the lesions, the ultimate score was decided by averaging the scores calculated by each cardiologist. SS1 and SS2 scores were obtained for each patient.

Statistical Analyses

The continuous variables were investigated using Kolmogorov-Smirnov and Shapiro-Wilk tests to determine whether or not they are normally distributed. Data was expressed as mean∓standart deviation for continuous variables and number and/or percentage for categorical variables. The univariate analysis of the study parameters, on the basis of their types and the fulfillment of the assumptions, were implemented using respective Chi Square, Continuity correction or independent t-test. For the multivariate analysis, the possible factors identified with univariate analysis were further entered into binary logistic regression to determine independent predictors of mortality. Hosmer-Lemeshow goodness of fit statistics were used to asses model fit. Finally, the receiver operating characteristics (ROC) curve analysis was implemented so as to assess whether the variables obtained through logistic regression analysis have any diagnostic role or not. In all statistical tests, $p<0.05$ was considered to indicate statistical significant. Statistical analysis of the study data was performed using SPSS version 21.0 software for Windows (IBM SPSS Statistics for Windows,Version 22.0. Armonk, NY: IBM Corp., USA).

Results

Demographic and clinical characteristics of the study population were given in Table 1. A total of 238 patients acute STMI patients was included in the study. Mortality occurred within the 6-month of study period in 25 patients (10.5%), while 213 patients (89.4%) remained alive at the 6th post-AMI month. There was statistically significant difference regarding gender distribution between the two groups (p=0.023). Male predominance was evident in the group without mortality [161 male (76%), 52 female (24%)]. On the other hand, gender distribution in the group with mortality was homogeneous [13 male (52%), 12 female (48%)]. The mean age of the group with mortality was greater than that of the group without mortality (68.11∓19.87 years and 60.49∓11.28 years, respectively; p=0.006). Glomerular filtration rate (GFR) was lower in the group with mortality, while white blood cell count (WBC), neutrophil count, C-reactive protein, Syntax I score and Syntax II score were significantly greater in the group with mortality, compared to the group without mortality (p<0.05). There was no significant difference with regard to the other demographic and clinical characteristics

between the two groups(p>0.05). Native thiol, total thiol, disulphide levels, and disulphide/native thiol, disulphide/total thiol and native thiol/total thiol ratios did not display any statistically significant difference between the two groups(p>0.05).

CAD,coronary arterial disease,GFR, glomerular filtration rate. WBC, white blood cell. Cholesterol Hgb, hemoglobin. Plt, platelet. C-RP, C-reactive protein. Hs-troponin High-Sensitivity Cardiac Troponin T Ck-Mb creatine kinase myocardial isoenzyme PCT: Platelecrite TG, triglyceride. T-Chol, total cholesterol. LDL-C, low-density lipoprotein cholesterol. HDL-C, high-density lipoprotein.

As for the cause of mortality, it was multiorgan system failure including acute renal insufficiency in two patients (0.8%), sudden cardiac death in 10 patients (4.2%), and cardiogenic shock in 13 patients (5.4%). In-hospital mortality occurred in10 patients (4.2%), while post-discharge mortality occurred in 15 patients (6.3%).

The demographic and the clinical variables revealed to be different between the two groups were analyzed further via bivariate logistic regression analysis with backward elimination, wherein Syntax II score, GFR and WBC emerged in the fifth step of the logistic regression analysis as the variables which predicted the mortality most precisely within the study population. Table 2 represents the results of the logistic regression analysis, together with pertinent odds ratios. The percentage correct score of the regression model was 92.4%. Moreover, according to the Hosmer and Lemeshow test, the positive predictive value of this regression model was found to very strong (X^2=1.448,p>0.05).

These three variables, namely the Stntax II score, GFR and WBC, which had been found to be significant predictor of mortality, were further evaluated through ROC curve analysis regarding whether we could obtain a cut-off value in the prediction of mortality among the study population. According to the ROC curve analysis, the optimal cut-off value to predict mortality was 42.7 for the Syntax II score (Figure 1). With this cut-off value, the Syntax II score had 79% sensitivity and 88.8% specificity to predict 6-month mortality among the survivors of acute STMI (AUC: 0.846; %CI: 0.681-0.902; p<0.01). Contrary to the Syntax II score, however, GFR and WBC were not anticipated to confer any cut-off value of diagnostic significance, as the area under curve for these variables did not reach the level of statistical

Table 1. Demographic and clinical characteristics of the study population

Variables	Group without mortality(n=213)	Group with mortality (n=25)	p
Gender(male,female ,%)	161(76%)/52(24%)	13(52%)/12(48%)	0.023
Age (Years)	60.49∓11.28	68.11∓19.87	0.006
Diabetes Mellitus (n,%)	66 (30%)	8(32%)	0.917
CAD (n,%)	31(14%)	3(12%)	0.966
Hypertension (n,%)	94(44%)	12(48%)	0.876
Hyperlipidemia (n,%)	54(25%)	6(24%)	0.882
Smoking(n,%)	106(49%)	12(48%)	0.867
Glucose (mg/dL)	129.6∓67.2	165.8∓91.5	0.088
GFR (mL/min/1,73-m2)	82.13∓18.68	63.11∓39.44	0.012
WBC (x109/L)	9.51∓2.96	12.64∓7.65	0.016
Hgb (gr/dL)	13.91∓1.74	13.46∓2.74	0.526
Plt (x109/L)	263.5∓91.4	276.3∓121.4	0.695
Neuthropil (x109/L)	6.25∓2.69	9.67∓7.38	0.004
Lymphocyte (x109/L)	2.27∓0.91	1.87∓1.38	0.235
Monocyte (x109/L)	0.77∓0.27	0.96∓0.78	0.111
C-RP (mg/dL)	1.28∓2.09	7.39∓8.83	<0.001
Hs-troponin pg/mL	3395∓10977	4930∓3806	0.696
Ck-Mb ng/mL	51.37∓71.29	56.81∓75.64	0.848
PCT (%)	0.27∓0.09	0.24∓0.04	0.407
Calcium mg/dL	9.27∓0.52	9.40∓1.28	0.575
Albumin gr/dL	4.02∓0.46	3.73∓0.58	0.087
TG (mg/dL)	172.4∓91.6	192.4∓109.6	0.576
T-Chol (mg/dL)	169.3∓42.2	183.4∓78.3	0.413
LDL-C (mg/dL)	94.2∓38.9	100.7∓58.5	0.680
HDL-C (mg/dL)	41.90∓10.46	44.14∓16.50	0.567
Total thiol (micromol/L)	225.3∓37.8	223.8∓34.9	0.930
Native thiol (micromol/L)	136.2∓24.5	136.8∓21.9	0.984
Disulphide (micromol/L)	44.38∓7.19	43.50∓6.95	0.644
Disulphide/Native thiol (%)	32.75∓2.35	31.85∓2.59	0.298
Disulphide/ Total thiol (%)	19.76∓0.86	19.43∓0.94	0.293
Native thiol/total thiol (%)	60.46∓1.73	61.13∓1.89	0.293
Syntax-1	19.12∓9.80	26.11∓8.06	0.029
Syntax-2	30.63∓9.79	50.13∓14.59	<0.001

Table 2. Binary logistic regresyon analysis of mortality and affecting variables.

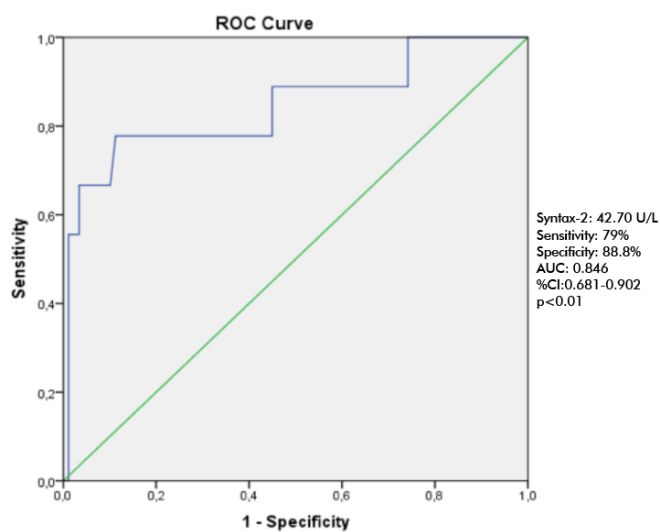|	Odds Ratio	95% Confidence Interval		p
		Lower	Upper	
Syntax -2	1.514	1.095	1.889	0,001
GFR	1.122	1.006	1.253	0,033
WBC	1.820	1.1168	2.836	0,008

GFR: glomerular filtration rate, WBC, white blood cell.

Figure 1. Receiver-operating curve depicting sensitivity and specificity of the Syntax II score in the prediction of 6-month mortality Discussion

Discussion

The main findings of our study can be summarized as follows: the admission thiol/disulphide status does not have any significant correlation with the long-term (6 months) all-cause mortality in acute STMI patients; the Syntax II score, WBC and GFR possess predictive value in the long-term mortality in acute STMI patients according to the bivariate logistic regression analysis; and, a Syntax II score >42.7 anticipate 6-month all-cause mortality with 79% sensitivity and 88.8% specificity in patients with acute STMI. To the best of our knowledge, this study is the first to assess the relationship between thiol/disulphide homeostasis and 6-month all-cause mortality in patients with STMI.

Thiols assist the bodily systems to withstand oxidative stress. Upon encountering the ROS, thiol groups of sulfur containing aminoacids become oxidized to transform into reversible disulphide molecules, thus subsiding the detrimental effects of the ROS. Subsequently, the disulphide bonds previously formed can readily be reduced back to its original thiol form with the help of the other anti-oxidant mechanisms within the body; thereby, a dynamic thiol/disulphide homeostasis has managed to be achieved. Previous in vitro studies indicated that lower thiol/disulphide homeostasis was likely to translate into abnormal cellular apoptosis or proliferation [13,14].

Previous studies have already unfolded that acute coronary syndrome is associated with lower thiol/disulphide homeostasis [15-17]. Sivri et al. [16] demonstrated lower total and native thiol levels as well as native thiol/total thiol ratio; however, greater disulphide/total thiol and disulphide/native thiol in patients with non-ST elevation myocardial infarction

(NSTMI), compared to the healthy controls. Kavakli et al. [15] investigated thiol/disulphide status in 128 STMI patients and reported a statistically significant decrease in admission serum total thiol, native thiol and disulphide levels, compared to 30 healthy controls. In another study conducted by Kundi et al. [17] and including 300 patients with acute coronary syndrome (150 STMI, 150 NSTMI), total thiol, native thiol and disulphide were found to be lower, compared to 150 healthy controls. On the other hand, disulphide/total thiol and disulphide/native thiol were significantly greater, compared to the controls.

Aside from the acute coronary syndrome itself, some other clinical conditions as diabetes mellitus[18], hypertension[19], stable coronary arterial disease[20], chronic kidney disease[21], autoimmune diseases [22-25] implicated in the development of an acute coronary syndrome were also suggested to be associated with lower thiol/disulphide homeostasis.

There are many stress factors, such as ischemia, volume and pressure overload, that may incline the cardiovascular system towards remodeling at cellular levels[26]. Furthermore, cardiovascular remodeling may in turn be related to increased mortality, since adaptive changes in the cardiovascular and coronary arterial system may translate into myocardial fibrosis, positive or negative vascular plaque remodeling and potentially irreversible myocardial or vascular functional deterioration [27,28]. Accordingly, an altered thiol/disulphide homeostasis is very likely to remain incapable of adequately withstanding the oxidative stress milieu like an AMI, and this situation may in part be held responsible with the inappropriate adaptive changes posing an extra risk for future mortality. Previous studies, in this regard, revealed findings supportive of this premise. In their study, Sivri et al. [16] found a negative correlation between native thiol and the rate of major adverse cardiovascular events (MACE), including mortality, non-fatal MI and acute heart failure, in patients with NSTMI. However, the other thiol/disulphide homeostasis-related parameters did not show such a correlation. In another study by Kundi et al. [29], in-hospital mortality was associated with both lower native thiol/disulphide ratio and higher Syntax I score. Akkuş et al. [30] suggested in their recent study that levels of admission native thiol and total thiol served as independent predictors of MACE, which had included acute coronary syndrome, stroke, and death and target vessel revascularization, during 6 months of follow-up of STMI patients. Contrary to the study by Kundi et al. [29], however, their study failed to yield an association of in-hospital mortality with neither native and total thiol levels nor native thiol/disulphide ratio. Aside from the afore-mentioned studies, our study merely investigated all-cause mortality

during 6-month follow-op of patients with STMI, and we did not find any correlation between the mortality and admission parameters related to the thiol/disulphide homeostasis. The reason for the lack of such an association can be attributed to the fact that we only evaluated the relationship of the mortality and the admission thiol/disulphide parameters, contrary to MACE in the previous studies.

This study should be interpreted in the light of some limitations. First, our study population is relatively small and future studies conducted on larger populations may yield correlation between the long-term mortality and admission thiol/disulphide status in STMI patients. Secondly, this is a single-center study and demographic, genetic and racial features of our patient cohort display distinctions from that of other centers. Third, we did not correlate our study findings with the other oxidative stress markers.

Conclusion

Admission serum native thiol level, total thiol level, disulphide level, native thiol/total thiol ratio, native thiol/disulphide ratio and total thiol/disulphide ratio cannot be used to identify patients with increased 6-month mortality among the patients with STMI. On the other hand, the Syntax II score, GFR and WBC show robust association with the 6-month mortality rates in the same patient population. However, further studies with larger cohots as well as longer follow-up periods may reveal different results.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

References

1. Roger VL, Weston SA, Gerber Y et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation 2010; 121: 863-69

2. Tu JV, Austin PC, Filate WA et al. Outcomes of acute myocardial infarction in Canada. Can J Cardiol 2003; 19: 893-901.

3. Tu JV, Donovan LR, Lee DS et al. Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. JAMA. 2009; 302: 2330-37

4. Jaganjac M, Cipak A, Schaur RJ and Zarkovic N. Pathophysiology of neutrophil-mediated extracellular redox reactions. Front Biosci (Landmark Ed). 2016; 21: 839-55.

5. Young IS and Woodside JV. Antioxidants in health and disease. J Clin Pathol 2001; 54: 176-86.

6. Turell L, Radi R and Alvarez B. The thiol pool in human plasma: the central contribution of albumin to redox processes. Free Radic Biol Med 2013; 65: 244-53

7. Sen CK and Packer L. Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr 2000; 72: 653-69

8. Jones DP and Liang Y. Measuring the poise of thiol/disulfide couples in vivo. Free Radic Biol Med 2009; 47: 1329-38

9. Thygesen K, Alpert JS, Jaffe AS et al. Third universal definition of myocardial infarction. Circulation 2012; 126: 2020-35

10. Quinones MA, Otto CM, Stoddard M et al. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002; 15: 167-84.

11. Ibanez B, James S, Agewall S et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77,

12. Erel O and Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem 2014; 47: 326-32

13. Circu ML and Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. Free Radic Biol Med 2010; 48: 749-62

14. Biswas S, Chida AS and Rahman I. Redox modifications of protein-thiols: emerging roles in cell signaling. Biochem Pharmacol 2006; 71: 551-64

15. Kavakli HS, Sezer AA, Yilmaz H et al. Thiol disulphide homeostasis in patients with acute myocardial infarction (AMI). J Pak Med Assoc 2018; 68: 1631-35.

16. Sivri S, Kasapkara HA, Polat M et al. Dynamic thiol/disulphide homeostasis and its prognostic value in patients with non-ST elevation-acute coronary syndromes. Kardiol Pol 2018; 76: 426-32

17. Kundi H, Ates I, Kiziltunc E et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med 2015; 33: 1567-71

18. Ates I, Kaplan M, Yuksel M et al. Determination of thiol/disulphide homeostasis in type 1 diabetes mellitus and the factors associated with thiol oxidation. Endocrine 2016; 51: 47-51

19. Ates I, Ozkayar N, Inan B et al. Dynamic thiol/disulphide homeostasis in patients with newly diagnosed primary hypertension. J Am Soc Hypertens 2016; 10: 159-66

20. Altiparmak IH, Erkus ME, Sezen H et al. The relation of serum thiol levels and thiol/disulphide homeostasis with the severity of coronary artery disease. Kardiol Pol 2016; 74: 1346-53

21. Rodrigues SD, Batista GB, Ingberman M, Pecoits-Filho R and Nakao LS. Plasma cysteine/cystine reduction potential correlates with plasma creatinine levels in chronic kidney disease. Blood Purif 2012; 34: 231-37

22. Dogru A, Balkarli A, Cetin GY et al. Thiol/disulfide homeostasis in patients with ankylosing spondylitis. Bosn J Basic Med Sci 2016; 16: 187-92

23. Lalwani P, de Souza GK, de Lima DS, Passos LF, Boechat AL and Lima ES. Serum thiols as a biomarker of disease activity in lupus nephritis. PLoS One 2015; 10: e0119947

24. Ates I, Altay M, Yilmaz FM et al. Dynamic thiol/disulfide homeostasis in patients with autoimmune subclinical hypothyroidism. Endocr Res 2016; 41: 343-49

25. Jaswal S, Mehta HC, Sood AK and Kaur J. Antioxidant status in rheumatoid arthritis and role of antioxidant therapy. Clin Chim Acta 2003; 338: 123-29.

26. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol. 2014; 11: 255-65, doi: 10.1038/nrcardio.2014.28.

27. Falk E, Nakano M, Bentzon JF, Finn AV and Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J 2013; 34: 719-28

28. Gaasch WH and Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. J Am Coll Cardiol 2011; 58: 1733-40

29. Kundi H, Erel O, Balun A, et al. Association of thiol/disulfide ratio with syntax score in patients with NSTEMI. Scand Cardiovasc J 2015; 49: 95-100

30. Akkus O, Topuz M, Koca H, et al. The relationship between low thiol levels and major adverse cardiovascular events after primary percutaneous coronary intervention in patients with STEMI. Turk Kardiyol Dern Ars. 2018; 46: 248-59