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

ABSTRACT

Aim: Acute ST-elevation myocardial infarction (STMI) is a significant determinant of mortality and long-term mortality rates have 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 intervention 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 19.12±9.80, p=0.029 for Syntax I; 50.13±14.59 vs 30.63±9.79, 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
Thiol/disulphide homeostasis and acute st-elevation myocardial infarction

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 antioxidant 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 antioxidant 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 evaluation 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±standard 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 assess 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: Plateletcrit 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 in 10 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 Syntax 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; 95%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 (g/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 g/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 regression analysis of mortality and affecting variables.

|                      | Odds Ratio | 95% Confidence Interval | p   |
|----------------------|------------|-------------------------|-----|
| Syntax-2             | 1.514      | 1.095 to 1.889          | 0.001 |
| GFR                  | 1.122      | 1.006 to 1.253          | 0.033 |
| WBC                  | 1.820      | 1.1168 to 2.836         | 0.008 |

GFR: glomerular filtration rate, WBC, white blood cell.
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-up 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 cohorts as well as longer follow-up periods may reveal different results.

**Declaration of conflict of interest**

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