The role of oxidative stress and inflammation in the early evaluation of acute non-ST-elevation myocardial infarction: an observational study

ST-yükselmesi olmayan akut miyokart enfarktüsünün erken değerlendirmesinde oksidatif stres ve enflamasyonun rolü: Gözlemsel bir çalışma

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Abstract

Objective: We aimed to assess the role of oxidative stress (OS) and inflammation in the early evaluation of initial acute non -ST -elevation myocardial infarction (NSTEMI) compared with unstable angina pectoris (USAP).

Methods: Forty-seven (54%) patients with NSTEMI and 40 (46%) with (USAP) were included in this cross-section observational study. We assessed the oxidative stress and inflammation parameters. Statistical analysis was performed using Fisher's exact test, Chi-square test, Mann-Whitney U test, Student's t-test, and Pearson correlation analysis for assess the correlations between variables.

Results: Plasma total oxidative stress (TOS) and OS index levels were significantly higher ($p<0.001$ for both comparisons), in patients with NSTEMI. In addition, white blood cell count (WBC) and high-sensitive C-reactive protein (hs-CRP) levels were significantly higher in patients with NSTEMI (respectively; $p<0.001$, $p=0.02$). Age, WBC and low- density lipoprotein cholesterol showed positive correlations with TOS level (Pearson correlation coefficient: $r=0.290$, $p=0.006$; $r=0.431$, $p<0.001$; $r=0.219$, $p=0.042$ respectively), and also age showed positive correlation with OS index (Pearson correlation coefficient; $r=0.246$; $p=0.021$). However, the values of the troponin I and creatine kinase-MB fraction did not differ between the two groups ($p>0.05$ for all).

Conclusion: TOS, OSI, WBC and CRP levels are significantly higher in NSTEMI subject. These data suggest that inflammatory processes and oxidative stress together play a role in the pathogenesis of acute NSTEMI. *(Anadolu Kardiyol Derg 2013; 13: 131-6)*

Key words: Oxidative stress, non -ST-elevation myocardial infarction, inflammation parameters

ÖZET

Amaç: Kararsız angina pectoris (USAP) ile karşılaştırıldığında ST-elevasyonsuz miyokart enfarktüsünün (NSTEMI) başlangıç değerlendirmesinde oksidatif stres ve enflamasyonun rolünü belirlemeyi amaçladık.

Yöntemler: Bu enine-kesitli gözlemsel çalışmaya NSTEMI bulunan 47 (%54) ve USAP bulunan 40 (%46) hasta dahil edildi. Çalışmamızda OS ve enflamasyon parametrelerini inceledik. İstatistiksel analizde Fischer's tam testi, Ki- kare testi, Student's t-testi, Mann-Whitney U testi ve değişkenler arasındaki ilişkiyi göstermek için Pearson korelasyon analizi kullanıldı.

Bulgular: NSTEMI olan olgularda, plazma total oksidatif stres (TOS) ve OS indeks düzeyleri belirgin olarak yüksek idi (her iki karşılaştırma için; $p<0.001$). Ayrıca NSTEMI olan olgularda beyaz küre sayısı (WBC) ve yüksek-duyarlıklı C-reaktif protein (hs-CRP) düzeyleri de belirgin olarak yüksek idi (sırası ile; $p<0.001$, $p=0.02$). Yaş, WBC ve düşük dansiteli lipoprotein kolesterol düzeyleri ile TOS düzeyi arasında pozitif bir korelasyon vardı (Pearson korelasyon katsayısı sırası ile; $r=0.290$, $p=0.006$; $r=0.431$, $p<0.001$; $r=0.219$, $p=0.042$). Ayrıca yaş OSI ile pozitif bir korelasyon gösterdi (Pearson korelasyon katsayısı; $r=0.246$; $p=0.021$). Fakat acil servise kabul sırasında troponin I ve CK-MB değerleri bakımından iki grup arasında belirgin fark yoktu (sırası ile; $p=0.297$, $p=0.522$).

Sonuç: USAP olan olgular ile kıyaslandığında, NSTEMI olgularında TOS, OSI, WBC ve hs-CRP düzeyleri belirgin olarak yüksektir. Bu veriler, enflamatuvar süreç ile oksidatif stresin beraber ST elevasyonu olmayan akut miyokart enfarktüsü patogenezinde rol oynadığını düşündürmektedir. *(Anadolu Kardiyol Derg 2013; 13: 131-6)*

Anahtar kelimeler: Oksidatif stres, ST elevasyonu olmayan akut miyokart enfarktüsü, enflamasyon parametreleri

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Introduction

In Western developed countries the atherosclerosis-related diseases, such as cardiovascular disease (CVD), remains so far the major cause of morbidity and premature death (1, 2). For this reason, atherosclerotic cardiovascular disease represents a major public health concern, and many efforts are addressed to better understand the mechanisms underlying this important pathology (2). Oxidative stress (OS) is the unifying mechanism for many CVD risk factors, which additionally supports its central role in CVD (3). OS is defined as a balance between the formation and elimination of free radicals. Any increase in the rate of free radical formation, or decrease in their elimination, can disrupt this balance, resulting in OS (4-6). Superoxide and other reactive oxygen species (ROS) are increased in arteries in several major cardiovascular diseases (7, 8). This finding led to one of the most intriguing hypotheses in contemporary vascular biology: ROS play a critical role in pathophysiology of atherosclerosis, hypertension, and other CVD (9).

Myocardial infarction (MI) is usually initiated by myocardial ischemia due to coronary artery obstruction. In the ischemic myocardium, ROS are generated, especially after reperfusion (10, 11). A causative association between oxidative stress and coronary artery disease (CAD) has been detected in several clinical studies (12, 13). However, there are no enough studies on the OS in ACS patients and its clinical significance. Because of differences have been reported in extent of myocardial damage between patients with acute non-ST-elevation MI (NSTEMI) and unstable angina (USAP) (14-17), the differences of TOS and inflammation markers also expected in these patients. Until now, status of OS and inflammation parameters has not been studied together in the NSTEMI and USAP. Therefore, in the present study, we aimed to assess the role of OS and inflammation parameters in the early evaluation of initial acute NSTEMI compared with USAP.

Methods

Study design

This study was designed as a cross-sectional observational study.

Study population

Eighty-seven consecutive subjects (mean age was 62.49±12.80 years, range 31-84 years) who were admitted to emergency department (ED) in Harran University Faculty of Medicine, between January 2012 and May 2012, with NSTEMI or USAP were enrolled in the study. Forty-seven subjects (54%) were diagnosed with NSTEMI, and 40 (46%) with USAP. NSTEMI and USAP were diagnosed with the electrocardiogram (ECG) interpretations; cardiac enzyme results and clinical findings according to established criteria (15). Presentation within ≤4 hours after symptom onset was required.

Exclusion criteria in our study were as follows: i) any coexisting cardiac disease, such as heart failure, arrhythmia and STEMI; ii) patients with chest pain present for more than 4 hours, iii) any evidence of liver, kidney or respiratory disease; iv) malignancy; v) any infectious, inflammatory or infiltrative disorder; vi) recent use (within 48 h) of any drug with anti-oxidant properties, such as nebivolol, carvedilol, vitamins E and C, and acetylcysteine; and vii) pregnant women, viii) surgical procedures or trauma in the preceding 3 months, ix) regular alcohol use or alcohol use within 48 hours.

The study protocol was carried out in accordance with the declaration of Helsinki (as revised in 1989) and was approved by the ethical committee of the Faculty of Medicine, Harran University, Şanlıurfa, Turkey. Written informed consent was provided by all participants, or from their legal guardians in the case of unconscious patients. Vital function monitoring of patients was performed prior to consent being requested.

Study protocol

Patients were provided with basic life support at presentation, and advanced life support if required. Blood samples were drawn from the antecubital vein of each subject immediately after presentation to the emergency department (ED). The possible influence of oxygen treatment on OS parameters, such therapy was considered to start after the collection of blood samples in patients. All participants were questioned about the character of their chest pain, its start time, smoking history, hypertension, and diabetes mellitus, which are risk factors for acute NSTEMI and the other types of acute coronary syndrome. The complete blood counts, biochemical parameters, and 12-lead ECG reports during the period of admission were received. For the diagnosis of NSTEMI, cardiac enzymes of the patients were repeated after 6 and 12 hours.

Study variables

The early oxidative-antioxidative status and inflammation parameters were the primary outcome variables, presence of NSTEMI and USAP-predictor variables. The baseline variables of study were factors include age, sex, body mass index (BMI), use of smoking, values of heart rate, admission time to ED, systolic (SBP) and diastolic (DBP) blood pressure, history of diabetes mellitus (DM), hypertension (HT) and coronary artery disease (CAD), triglycerides (TG) and low-density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) values. In addition, troponin I and creatine kinase MB fraction (CK-MB) values were recorded.

Assessments of oxidative status

Blood samples were immediately placed on ice 4°C. Plasma was separated from the cells by centrifugation (Hettich Lab Technology, Tuttlingen, Germany) at 2509 *g* for 10 min and stored at -80°C until analysis. Plasma total oxidative stress (TOS) and total antioxidant status (TAS) were assessed using an automated measurement method, as described previously (18, 19).

The TOS of serum was determined using a novel automated measurement method, also developed by Erel (18). Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundant in the reaction medium. The ferric ion generates a colored complex with Xylenol Orange in an acidic medium. Color intensity, which can be measured spectrophotometrically, is related to the quantity of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide and the results expressed in terms of micro-molar hydrogen peroxide equivalents per liter (mmol H_2O_2 equiv./L).

Serum TAS was determined using a novel automated measurement method, developed by Erel (19). By this method, hydroxyl radical, the most potent biological radical, is produced. In the assay, ferrous ion solution, present in Reagent 1, is mixed with hydrogen peroxide, which is present in Reagent 2. Sequentially-produced radicals like the brown-colored dianisidinyl radical cation, produced by the hydroxyl radical, also are potent radicals. Using this method, the anti-oxidative effect of the sample against potent free-radical reactions, which are initiated by the produced hydroxyl radical, can be measured. The assay has excellent precision values, of greater than 97%. The results are expressed as mmol Trolox® (6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid) equivalents/L.

The OS index (OSI) is defined as the ratio of the TOS to TAS level, expressed as a percentage. For the calculation, TAS units were changed to mmol/L, and the OSI value calculated according to the following Formula (20): OSI (arbitrary units)=TOS (μmol H_2O_2 equivalents/L)/TAS (mmol Trolox® equivalents/L) x 10^{-1}

Assessments of cardiac markers, complete blood count and routine biochemical tests

Blood samples taken from both NSTEMI and USAP at admission to the ED, included routine biochemical tests (Aeroset, Abbott, Abbott Park, Illinois, USA), cardiac markers (CK-MB; reference weight 0.18-5 ng/mL, and troponin I; reference weight 0.02-0.06 ng/mL) with electrochemiluminescence, Siemens Immulite 2000 device] and high-sensitive C-reactive protein (hr-CRP) (Roche/Hitachi Cobas system, Roche Diagnostics GmbH, D68298 Mannheim Germany) which were studied in the biochemistry laboratory after blood samples centrifuged with a cycle of 3500 in 10 minutes. The serum samples were preserved at -80°C until the tests could be completed. The precipitate was measured in immunoturbidimetric and results were expressed as mg/L. White blood cell count (WBC) was counted (range 4-10x10^9/L) using Cell Dyn Ruby analyzer with laser scatter method (Abbott Laboratories Diagnostic Division, Abbott Park, IL 60064 USA).

Statistical analysis

All calculations were performed using the SPSS 11.5 software package (SPSS Inc, Chicago IL, USA). Continuous variables are presented as mean±standard deviation (SD) and categorical ones as actual numbers and percentages. Normality of distribution for continuous variables was assessed using the Kolmogorov-Smirnov test. Comparisons between categorical variables were performed using the Chi-square test or Fischer's exact test, as appropriate. Comparisons between groups were carried out using Student's t-test or the Mann-Whitney U test according to the normality of distribution. Findings were considered statistically significant at the 0.05 level.

Pearson correlation test was used to evaluate correlations between OS parameters (TOS, TAS, OSI) level and some clinical data [Age, WBC, and hs-CRP]. A p value <0.05 was considered statistically significant.

Power analysis: On the basis of the average values of TOS (NSTEMI 47, USAP 40, alpha degree of freedom as 0.05) the two tailed power was 100% in the study.

Results

Clinical and demographic features

Of eighty-seven patients in the study, 47 (54%) had NSTEMI and 40 (46%) had USAP. Thirty-two members of the NSTEMI group (68%) were male and 15 (32%) were female, mean age was 62.49±12.80 (range, 31-84 years). In the USAP group, 28 cases (70%) were male and 12 (30%) were female, mean age was 59.30±9.92 years (range, 40-76 years). A statistically significant difference between the two groups with respect to age and sex was not observed.

Angiography was performed to 59% (28/47) of the patients with NSTEMI. The overall mortality rate of NSTEMI patients was 10.6% (5/47 patients). There were no statistically significant differences between the two groups with regard to the BMI, rates of DM, DBP, DBP and cigarette smoking. The demographic and clinical data for the two comparison groups are shown in Table 1.

Assessment of TOS, TAS and OSI

The time interval between onset of chest pain and ED visits was 1-4 hours. Mean admission time was 2.01±0.12 hours (1-4 hours). Plasma TOS and OSI levels were significantly higher (p<0.001 for both comparisons), in patients with NSTEMI compared with USAP subjects. While plasma TAS levels were lower in patients with NSTEMI than USAP subjects (Table 2), there were no significant between-groups differences (p=0.215).

Assessment of biomarkers of myocardial damage, inflammation and lipids

The values of the troponin I and CK-MB at ED admission were not significantly different between the two groups (respectively; p=0.297, p=0.522). WBC and hs-CRP levels were significantly higher in patients with NSTEMI (respectively; p<0.001, p=0.02). Plasma LDL-C and TTG levels were higher in patients with acute NSTEMI compared with USAP subjects, too (p<0.05 for both comparisons) (Table 3). However, there were not significant relationship between the two groups (respectively; p=0.239, p=0.682).

Table 1. Demographic and clinical characteristics

Variables	NSTEMI (n=47)	USAP (n=40)	* p
Age, years	62.49±12.80	59.30±9.92	0.203
Gender, F/M	15/32	12/28	1.00
BMI, kg/m^2	29.45±2.64	28.61±1.82	0.084
CAD, +/–	16/48	13/40	0.734
DM, +/–	8/47	5/40	0.557
SBP, mmHg	110.83±14.76	110.10±15.82	0.825
DBP, mmHg	81.531±13.33	79.82±12.88	0.361
HR, beats/min	108.26±16.95	106.18±13.46	0.533
SC, +/–	13/47	11/40	1.00
Admission time, hour	2.01±0.12	2.19±0.16	0.499

Data presented as mean±SD (standard deviation) or n of patients,
*Mann-Whitney U test, Student t test, Chi-square test
BMI - body-mass index, CAD - coronary artery disease, DBP - diastolic blood pressure, DM - diabetes mellitus, HR - heart rate, NSTEMI - non-ST-elevation myocardial infarction, SBP - systolic blood pressure, SC - smoking cigarette, USAP - unstable angina pectoris

Table 2. Oxidative stress parameters

Variables	NSTEMI (n=47)	USAP (n=40)	*p
TOS, µmol H_2O_2 equiv./L	66.89±16.11	49.10±7.21	<0.001
	65 (42.6-109.8)	49 (32.5-65.7)	
TAS, mmol Trolox equiv./L	0.78±0.26	0.84±0.18	0.215
	0.75 (0.35-1.22)	0.86 (0.30-1.14)	
OSI, arbitrary unit	9.66±4.08	6.34±2.85	<0.001
	8.8 (4.0-19.7)	5.9(3.08-21.6)	

Data are presented as mean±SD and median (min-max) values
*Mann-Whitney U test
NSTEMI - non-ST-elevation myocardial infarction, OSI - oxidative stress index, TAS - total antioxidant status, TOS - total oxidant status, USAP - unstable angina pectoris

Age, WBC and LDL-C showed positive correlations with TOS level (r=0.290, p=0.006; r=0.431, p<0.001; r=0.219, p=0.042 respectively). In addition, age showed positive correlation with OSI (r=0.246; p=0.021). But neither were significantly related to TAS (Table 4).

Discussion

In this study, our findings suggested that the levels of OS and inflammation parameters are higher in the NSTEMI patients than in the USAP patients. Thus we demonstrated the potential role of inflammation parameters and OS for early outcome of the patients with STEMI in ED. Demographic characteristics for the two comparison groups were similar in our study. There were no statistically significant differences between the two groups with regard to age, gender, BMI, the rates of diabetes mellitus, the rates of diabetes CAD, SBP, DBP and HR.

The development of OS biomarkers has helped establish that ROS and oxidative events are part of the pathophysiology of

Table 3. Laboratory characteristics

Variables	NSTEMI (n=47)	USAP (n=40)	* p
LDL-C, mg/dL	139.64±28.98	133.75±16.40	0.239
	136 (99-2109)	133(100-170)	
TG, mg/dL	104.40±44.52	100.90±34.84	0.682
	100 (67-189)	103 (39-191)	
WBC, x10^9/L	12.92±4.66	6.86±4.77	<0.001
	12.3(11.9-24.5)	6 (5.4-34)	
hs-CRP, mg/dL	2.51±0.84	1.21±0.82	0.024
	0.02 (0.10-26)	0.01 (0.30- 3.0)	
Troponin I, ng/dL	0.49±0.23	0.33±0.10	0.297
	0.02 (0.01-1.09)	0.01 (0.01-0.30)	
CK-MB, ng/dL	1.85±0.31	1.78±0.37	0.522
	1.2 (0.20-12)	1.0 (0.20-11)	

Data are presented as mean±SD and median (min-max) values
*Mann-Whitney U test
CK-MB - creatine kinase-myocardial band isoform, hs-CRP - high-sensitive C-reactive protein, LDL-C - low-density lipoprotein-cholesterol, NSTEMI - non-ST-elevation myocardial infarction, TG - triglycerides, USAP -unstable angina pectoris, WBC - white blood cells

Table 4. Correlation between oxidative stress and clinical variables

	AGE	WBC	hs-CRP	LDL
TOS	r=0.290; p=006**	r=0.431; p<0.001**	r=0.084; p=0.438	r=0.219; p=0.041*

Pearson correlation analysis
*Correlation is significant at the 0.05 level (2-tailed),
**Correlation is significant at the 0.01 level (2-tailed)
hs-CRP - high-sensitive C-reactive protein, LDL-C - low-density lipoprotein-cholesterol, OSI - oxidative stress index, TAS - total antioxidant status, TG - triglycerides, TOS - total oxidant status, WBC - white blood cells

CVD. It remains to be seen if consideration of these ROS-sensitive biomarkers can add clinically important information to patient care (21). ROS and antioxidants play a major role in both atherosclerosis and myocardial damage and preservation (22). Previously, increased ROS flux has been shown to damage myocytes, impair contractile function, and contribute to capillary leakage (23). Chandra et al. (24) demonstrated that there were elevated superoxide anion, malonyldialdehyde, and glutathione reductase levels and reduced superoxide dismutase and catalase levels in USAP and acute MI cases. Gupta et al. (25) measured the levels of antioxidants in patients with ischemic heart disease. It was found that plasma TOS and OSI levels were significantly higher in the NSTEMI at the admitted to ED than in the USAP subjects. Thus, our data indicated that patients in the study sample were exposed to potent OS and that the markers reflected OS. However, it is not clear whether oxidative stress is a direct cause of NSTEMI or the result of several metabolic pathways associated with myocardial damage.

Inflammation is a critical factor in the pathophysiology of atherosclerosis and its thrombotic complications (26).

Population-based studies suggest that the assessment of circulating inflammatory markers may facilitate cardiovascular risk stratification among healthy individuals (27). Accumulating evidence has also established the role of inflammatory biomarkers in the prognosis of patients with ACS (28). Brunetti et al. (29) reported that plasma CRP concentrations showed a different release curve with Q-wave AMI in comparison with non Q-wave AMI and patients with USAP. Similarly, in our study, the hs-CRP and WBC levels at admission was significantly higher in the NSTEMI than the USAP subjects. This suggests that it might be influenced by the early myocardial tissue infarction. Moreover, in the present study, there were also a strong correlation between the TOS and WBC. OS with metabolic and inflammatory process, may be caused to myocardial infarction. Therefore, it was hypothesized that a repeated measurement of hs-CRP levels in CAD patients could help to discriminate those at high risk of further events (30).

Considering that management strategies for the acute phase of MI, with emphasis on early treatment, are essential to reduce the morbidity and mortality associated with ischemic myocardial disease. However, there is still controversy regarding the literature on how time of presentation to the ED and delays in care may influence effective treatment (31, 32). Troponin has become the preferred cardiac biomarker with respect to the diagnosis of acute MI (33). This serum protein of cardiac cell necrosis appears 4 to 12 hours after symptom onset (34). To avoid missing early myocardial damage in patients with normal or nondiagnostic ECG, physicians routinely employ the use of serial troponin measurements initially on arrival to the ED and subsequently at a time frame of 6 to 12 hours after the onset of ischemic symptoms (35). In the present study, the average admissions time of patients at the ED was 2.83±0.82 hours. Troponin I and CK-MB enzyme levels were within normal limits during the admitted to ED and there was no significant difference between the NSTEMI and USAP subjects. In the same time the measured level of TOS at admission was significantly higher in the NSTEMI group. Measurement of oxidative stress parameters with the Erel method and measurement of inflammatory parameters that results in 10 minutes, may be stimulant for early diagnosis of NSTEMI and also may be help the clinical outcomes of these patients.

Study limitations

This study has several potential limitations. First, the present study was performed in a single department, and we were able to provide data containing only one-time point measurement for OS and inflammation parameters from each patient. Blood samples were taken when the subjects admitted to the ED. For diagnosis of NSTEMI, cardiac enzymes of the patients were repeated after 6 and 12 hours. However, measurement of OS and inflammation parameters were not repeated at these hours. If verified in a larger multicenter study cohort, these findings could provide practical assistance to physicians regarding the best outcome options for NSTEMI. Second, our study was limited to assessing in-ED outcomes, and did not assess differences over longer periods. Third, despite troponin T remains to be the gold standard for the diagnosis of NSTEMI, we have investigated consecutive troponin I measurements because of it is solely available as a specific cardiac serum biomarker in our hospital's biochemistry laboratory.

Conclusion

TOS, OSI, WBC and CRP levels are significantly higher in NSTEMI subjects, when compared to USAP subjects. These data suggest that inflammatory processes and oxidative stress together play a role in the pathogenesis of acute NSTEMI. It is therefore important to identify reliable biomarkers allowing us to monitor OS status. These also may lead to improved understanding of acute NSTEMI pathogenesis and development of new therapeutic strategies.

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