The relation between intensity and complexity of coronary artery lesion and oxidative stress in patients with acute coronary syndrome

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ABSTRACT

Objective: Oxidative stress plays a major role in the development of atherosclerosis. However, the relationship between oxidative stress and complexity and intensity of coronary artery disease is less clear. The aim of this study is to assess the relationship between oxidative stress markers and the complexity and intensity of coronary artery disease in patients with acute coronary syndrome (ACS).

Methods: Sixty-seven consecutive patients with an early phase of ACS (<3 h) were included in this single-centre, cross-sectional, prospective study. Syntax and Gensini scores were calculated based on angiographic findings. Patients were divided into two CAD complexity groups according to their Syntax scores: low SYNTAX score (<22) and moderate to high SYNTAX score (>=22). Likewise patients were divided into two CAD severity groups according to the median Gensini score of 64: less intensive CAD with Gensini score (<64) and intensive CAD with Gensini score >=64. Blood samples were taken in 1 hour within administration in order to measure total oxidative status (TOS) and total antioxidant capacity (TAC) levels determined by Erel method. Oxidative stress index (OSI) was calculated by TOS /TAC.

Results: There was no significant difference between the two SYNTAX groups for oxidative stress markers. Median TOS and OSI values were significantly high in the intensive CAD group (p=0.005, p=0.04, respectively). The Gensini score was positively correlated with TOS and OSI (p=0.003, p=0.02, respectively).

Conclusion: Oxidative stress markers may be considered supportive laboratory parameters related to CAD intensity but not complexity in ACS patients. *(Anatol J Cardiol 2015; 15; 795-800)*

Keywords: acute coronary syndrome, oxidative stress, coronary artery disease, total antioxidant capacity, total oxidative stress, oxidative stress index, myocardial infarction

Introduction

Reactive oxygen radicals (ROS) and antioxidants are in equilibrium in the human body. The disturbance of this equilibrium by the increase of ROS and/or decrease of antioxidant capacity causes oxidative stress (OS). Oxidative stress is a key mechanism in the occurrence and progression of atherosclerosis (1). Macrophages that are loaded with oxidized LDL and other lipids cause the accumulation of foam cells and fatty streaks in the environment of oxidative stress (2, 3). On the other hand, these macrophages produce more ROS by causing a radical chain reaction and secrete various growth factors that lead to progression of atherosclerosis (4). It is widely accepted that the occurrence of oxidative stress with a disturbance in the balance between ROS and antioxidants promotes coronary artery disease (CAD) and increases plaque vulnerability (5). Therefore, we studied patients with ACS. The measurement of serum concentrations of various oxidants and antioxidants separately is not practical, because it is time-consuming, complicated, and expensive and requires vigorous effort. Total antioxidant capacity (TAC), total oxidative stress (TOS), and oxidative stress index (OSI) reflect the equilibrium between oxidation and antioxidation. OSI is the ratio of TOS to TAC and an indicator of OS degree. Measurement of total antioxidant capacity is an indicator of the activity of all antioxidants, while TOS is an indicator of total oxidative stress. This is a very useful parameter to show true oxidative stress (6-9).

Oxidative stress plays a major role in the etiopathogenesis of atherosclerosis. However, the relationship between oxidative stress and complexity and intensity of coronary artery disease

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in acute coronary syndrome (ACS) patients is less clear. The aim of this study is to evaluate the relationship between oxidative stress markers (TAC, TOS, OSI) and the complexity and intensity of coronary artery disease in patients with ACS by using SYNTAX and Gensini scores.

Methods

This was a single-center, cross-sectional, prospective study conducted between January 2010 and May 2012 in Ahi Evren Training and Research Hospital, Trabzon, Turkey. We enrolled 125 patients undergoing coronary angiography with ACS. Patients who had cardiovascular disease (CAD, peripheral artery disease, cerebrovascular disease), renal disease (creatinine ≥2.5 mg/dL), malignancy, active infections, and late admission (>3 h from symptom onset) were excluded. Thus, 58 patients were excluded, and the remaining 67 patients (mean age 62±10 years; 53 males) constituted the study population. The average time from symptoms to blood taken was approximately 3 hours. The patients were evaluated on detailed clinical backgrounds, drugs used, findings of physical examinations, and smoking.

The study protocol conforms to the principles of the Declaration of Helsinki and is approved by local Ethic Committee. Informed consent of all patients was obtained for participation in the study.

Blood samples

Peripheral venous blood samples of the patients were obtained from a cubital vein into heparinized blood tubes within 1 hour of admission, before coronary angiography and intervention. The plasma was separated from the cells by centrifugation at 3000 rpm for 10 min and stored at -80°C until the day of biochemical analysis.

Measurement of total oxidant status (TOS), total antioxidant capacity (TAC), and calculation of oxidative stress index (OSI)

TOS and TAC levels were determined using a method previously described by Erel (9, 10) and were calculated in μmol H_2O_2 equivalent/L and mmol Trolox equivalent/L, respectively. These methods are automatic and colorimetric. The total antioxidant capacity measurement method is based on the bleaching of the characteristic color of a more stable 2,2'-azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) (ABTS) radical caption by antioxidants. The total oxidant status method is based on the oxidation of ferrous ion to ferric ion in the presence of various oxidant species in an acidic medium and the measurement of the ferric ion by xylenol orange. The TOS/TAC ratio was used as OSI. To perform the calculation, the unit of TAC, mmol Trolox equivalent/L, was converted to μmol Trolox equivalent/L, and OSI was calculated as follows: OSI = [(TOS, μmol H_2O_2 equivalent/L)/(TAC, μmol Trolox equivalent/L) x 100].

Coronary angiography and intensity and complexity of CAD

All patients underwent coronary angiography within 48 hours. The average time from symptoms to coronary angiography was approximately 6-8 hours. The intensity of coronary atherosclerosis in patients was assessed using the Gensini score (11), which grades the narrowing of the lumen of the coronary arteries as 1 for 1%-25% narrowing, 2 for 26%-50% narrowing, 4 for 51%-75% narrowing, 8 for 76%-90% narrowing, 16 for 91%-99% narrowing, and 32 for total occlusion. This score is then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree; for example: 5 for the left main coronary artery, 2.5 for the proximal left anterior descending (LAD) coronary artery or proximal left circumflex (LCX) coronary artery, 1.5 for the mid-region of LAD, and 1 for the distal LAD or mid-distal region of the LCX. The Gensini score was expressed as the total of the scores for all coronary arteries.

The complexity of CAD was assessed by the synergy between percutaneous coronary intervention with the Taxus and Cardiac Surgery Study (SYNTAX) score (12). The scores were calculated based on angiographic findings by two operators who were blinded to other parameters.

Statistical analysis

Continuous variables were tested for normal distribution by the use of the Kolmogorov-Smirnov test. Variables not normally distributed were expressed as medians (interquartile ranges). Normally distributed continuous variables were expressed as mean±standard deviation. Categorical variables were summarized as frequency percentages and absolute numbers. Patients were dichotomized according to the median value of the Gensini score. Likewise, a cut-off value of 22 for the SYNTAX score was used to group patients into low SYNTAX and moderate-to-high SYNTAX groups. The means for normally distributed continuous variables were compared by independent samples t-test. Skew-distributed continuous variables were compared using the Mann-Whitney U test. Pearson's x^2-test was used to compare categorical variables. Correlation of Gensini and SYNTAX score with oxidative stress markers was assessed by Pearson or Spearman's correlation analysis, as appropriate. SPSS software (Statistical Package for the Social Sciences, version 15.0, SSPS Inc., Chicago, IL, USA) was used for all statistical calculations. P values <0.05 were considered statistically significant.

Results

Sixty-seven patients with ACS were admitted to our study [mean age 62±10 years; 53 males (79.1%)]. Forty-three (64.2%) patients had unstable angina pectoris (USAP), 14 (20.9%) patients had non-ST elevated myocardial infarction (NSETMI), and 10 patients (14.9%) had ST elevated myocardial infarction (STEMI). All patients were diagnosed with CAD for the first time. The general demographic and clinical characteristics of the patients are summarized in Table 1.

SYNTAX scores of all patients were calculated in order to determine CAD complexity. Thirty-seven (55.2%) subjects displayed a low SYNTAX score (<22), and 30 (44.8%) subjects had

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Table 1. Baseline characteristics of the study population (n=67)

Age, years	62±10
Male/female, n (%)	53 (79.1%)/14 (20.9%)
BSA, m²	1.8 (1.4-1.9)*
Diabetes mellitus, n (%)	16 (23.9%)
Hypertension, n (%)	44 (65.7%)
PAD, n (%)	2 (3%)
Smokers, n (%)	23 (34.3%)
Statin use, n (%)	16 (23.9%)
ACEI/ARB use, n (%)	23 (34.3%)
Beta-blocker use, n (%)	17 (25.4%)
Nitrate use, n (%)	6 (9%)
LDL-cholesterol, mg/dL	134.1±34.4
Urea, mg/dL	39.3±12.6
Creatinine, mg/dL	0.94±0.35
SYNTAX score	22.1±9.6
Gensini score	70.4±35.9

ACEI/ARB - angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BSA - body surface area; LDL - low-density lipoprotein; PAD - peripheral arterial disease. *Data expressed as median (interquartile range)

Table 2. Comparison of clinical characteristics and serum oxidative markers in low and moderate-high SYNTAX scores

	Low SS (<22) (n=37)	Moderate/high SS (≥22) (n=30)	P
Age, years	59.5±9.5	65.1±9.9	0.02
Male gender	29	24	NS
BSA, m²	1.8 (1.4-1.9)	1.8 (1.3-1.9)	NS*
Diabetes mellitus, n	8	8	NS
Hypertension, n	26	18	NS
PAD, n	0	2	NS
Smokers, n	12	11	NS
Statin use, n	10	6	NS
ACEI/ARB use, n	15	8	NS
Beta-blocker use, n	12	5	NS
Nitrate use, n	6	0	NS
LDL-cholesterol, mg/dL	136.5±34.2	131±35.1	NS
Urea, mg/dL	38 (31.2-47.7)	38 (35-41)	NS*
Creatinine, mg/dL	0.95±0.41	0.92±0.25	NS
TOS, µmol H_2O_2 equivalent/L	7.8 (6-10.8)	10.2 (5.8-17.7)	0.1*
TAC, µmol Trolox equivalent/L	1.44±0.49	1.47±0.53	0.8
OSI	0.56 (0.37-0.88)	0.68 (0.34-1.55)	0.3*

ACEI/ARB - angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BSA-body surface area; LDL - low-density lipoprotein; NS - non-significant; OSI - oxidative stress index; PAD - peripheral arterial disease; SS - SYNTAX score; TAC - total antioxidant capacity of plasma; TOS - total oxidant status. *Skew-distributed continuous variables were compared using Mann-Whitney U test

Table 3. Comparison of clinical characteristics and serum oxidative markers in groups 1 and 2

	Group 1 (GS <64) (n=32)	Group 1 (GS ≥64) (n=35)	P
Age, years	59.2±9.2	64.5±10.2	0.03
Male gender	25	28	NS
BSA, m²	1.8 (1.6-1.9)	1.8 (1.0-1.9)	NS*
Diabetes mellitus, n	8	8	NS
Hypertension, n	19	25	NS
PAD, n	0	2	NS
Smokers, n	12	11	NS
Statin use, n	7	9	NS
ACEI/ARB use, n	11	12	NS
Beta-blocker use, n	9	8	NS
Nitrate use, n	3	3	NS
LDL-cholesterol, mg/dL	130±36.1	138.1±32.7	NS
Urea, mg/dL	38 (31-45.5)	38 (32-43)	NS*
Creatinine, mg/dL	0.96±0.41	0.91±0.27	NS
TOS, µmol H_2O_2 equivalent/L	6.8 (5.4-10.2)	10.65 (6.59-16.59)	0.005*
TAC, µmol Trolox equivalent/L	1.46±0.5	1.45±0.51	0.93
OSI	0.52 (0.31-0.77)	0.68 (0.40-1.50)	0.04*

ACEI/ARB - angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BSA - body surface area; GS - Gensini score; LDL - low-density lipoprotein; NS - non-significant; OSI - oxidative stress index; PAD - peripheral arterial disease; TAC - total antioxidant capacity of plasma; TOS - total oxidant status. *Skew-distributed continuous variables were compared using Mann-Whitney U-test

moderate to high SYNTAX scores (≥22). There was no significant difference between the two groups except age for all parameters, including oxidative stress markers (Table 2 and Fig. 1). Patients in the medium-high SYNTAX score (≥22) group were older than the others (p=0.02).

We calculated Gensini scores of the patients to determine CAD intensity. The median Gensini score of the patients was 64, and according to this value, patients were separated into two groups: less intensive CAD (group 1, Gensini <64) and intensive CAD (group 2, Gensini ≥64). Median (interquartile range) TOS and OSI values were significantly high in the intensive CAD group [6.8 (5.4-10.2) vs. 10.65 (6.59-16.59), p=0.005 and 0.52 (0.31-0.77) vs. 0.68 (0.40-1.50), p=0.04, respectively] (Fig. 2). Besides, the patients in the intensive CAD group were older than the others (59+9.2 vs. 64.5+10.2, p=0.03). There was no significant difference with regards to the other parameters (Table 3). A significant positive correlation was observed in the correlation analysis between Gensini score and TOS and OSI (r=0.353, p=0.003 and r=0.276, p=0.02; respectively).

Discussion

We aimed to determine the relationship between oxidative stress markers (TAC, TOS, OSI) and the complexity and intensity

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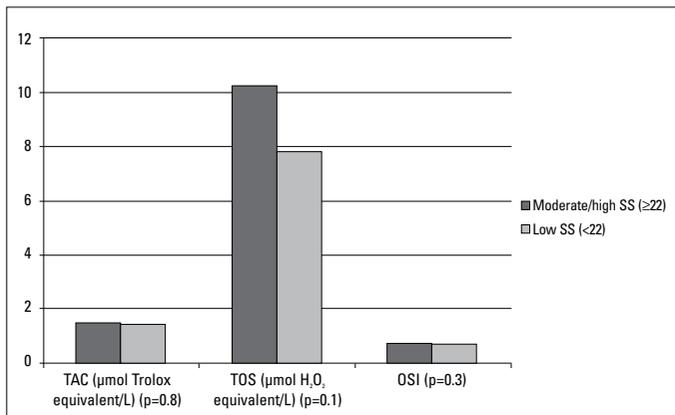Anatol J Cardiol 2015; 15: 795-800

Figure 1. Oxidative stress markers [total antioxidant capacity (TAC), total oxidative stress (TOS), and oxidative stress index (OSI)] in subjects with moderate to high (≥22) and low (<22) SYNTAX score (SS)
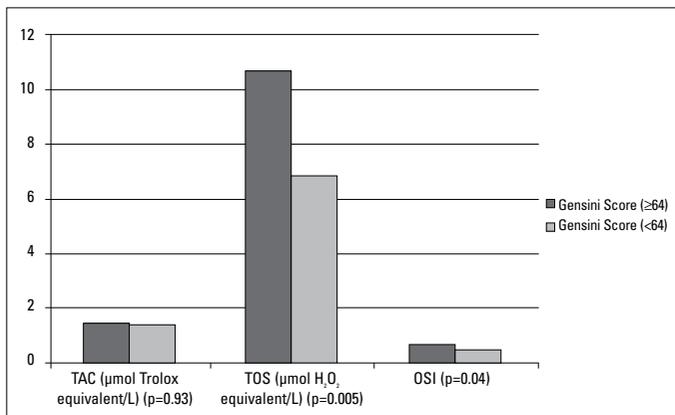

Figure 2. Oxidative stress markers [total antioxidant capacity (TAC), total oxidative stress (TOS), and oxidative stress index (OSI)] in subjects with intensive CAD (Gensini score ≥64) and less intensive CAD (Gensini score <64)

of coronary artery disease in patients with acute coronary syndrome (ACS). As far as we know, this article is the first in the literature that evaluates the relationship between oxidative stress markers and the complexity and intensity of CAD together. We enrolled only first-time CAD patients, because the treatment and interventions of CAD could alter Gensini and SYNTAX scores. It was shown that epicardial fat thickness and metabolic syndrome were associated with coronary atherosclerotic burden according to Gensini and SYNTAX scores (13, 14). In addition, Gensini and SYNTAX scores reflect the risk of major adverse cardiac and cerebrovascular events (MACCE) (15). We have not found any relation between oxidative stress markers and the complexity of CAD, determined according to SYNTAX score. However, there was a significant relation between oxidative stress markers and the intensity of CAD determined according to Gensini score. TOS and OSI levels were significantly higher in the intensive CAD group than in the less intensive CAD group. In addition, CAD intensity demonstrated a significant and positive correlation with oxidative stress markers.

Oxidative stress generally occurs with an increase of ROS and a disturbance in the oxidant-antioxidant balance in favor of oxi-

dants. ROS causes oxidation of thiol groups and peroxidation of lipids by modifying proteins and phospholipids. These derived oxidized products lead to an inflammatory response by activation of complement and leukocytes and secretion of cytokines and adhesion molecules (16-18). Oxidative stress and inflammation are closely associated with stabilization of the atherosclerotic plaque and ACS (19). The inflammatory cascade stimulated by ROS and oxidation of low-density lipoprotein (LDL) lead to the formation of macrophage-derived foam cells, proliferation in vascular smooth muscle cells, activation of vascular matrix metalloproteinase, and extracellular matrix damage in the affected region. In turn, this may cause atherosclerotic plaque rupture (20, 21). Ehara et al. (22) pointed out high plasma oxidized-LDL levels in ACS patients. The relation of oxidative stress with CAD has been proven convincingly in various studies (5). Akçay et al. (23) showed that the level of paraoxonase-1 (PON-1), which protects LDL against lipid peroxidation, in patients with metabolic syndrome (MetS) is lower than in healthy controls. Also, a negative correlation between PON-1 and Gensini score was determined in MetS patients. Our study is also supportive of these findings. We determined a positive relation between CAD intensity determined according to Gensini score (atherosclerotic plaque burden) and oxidative stress markers in patients with ACS. There are very few articles in the literature about the indirect evaluation of the intensity and complexity of CAD and oxidative stress markers (TAC, TOS, and OSI). One of these, Demirbağ et al. (24), compared plasma TAC and TOS values and Gensini scores of 30 patients with coronary artery bypass who underwent coronary endarterectomy with 30 healthy controls. In contrast to our study, while Gensini score was not determined to be related to TOS, it presented a negative correlation with TAC. In a study performed with rats, Yazıcı et al. (25) determined that although oxidative markers increased in the early phase of ischemia (2nd hour), they decreased significantly in prolonged ischemia. They attributed this to collaterals those developed in ischemia and destruction in ischemic cells. Kaneda et al. (26) showed that plasma levels of advanced oxidation protein products (AOPPs) were significantly higher in patients with coronary artery disease than in those without it. AOPP levels correlated with severity score of CAD according to the Gensini scoring system. Azumi et al. (27) observed that the generation of ROS was significantly higher in unstable angina pectoris patients compared with stable angina patients. While our study was performed with ACS patients during application (blood samples were taken within 1 hour), Demirbağ et al. (24) excluded ACS patients and included only stable CAD patients in their study.

In another study, Aksoy et al. (28) evaluated the relation between TAC, TOS, OSI, and SYNTAX score in young patients with acute myocardial infarction who smoked and found a positive correlation between SYNTAX score and TOS and OSI. We did not determine such a relation in our study. The reason for not determining this relation might be the exclusion of many factors that have no relation with atherosclerosis while calculating SYNTAX score (anatomic factors that determine the compatibility to percutaneous intervention, such as the presence of an ostial lesion,

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angle of the lesion, whether there is a bifurcation/trifurcation lesion, existence of calcification, vessel tortuosity…).

The treatment approach in ACS patients, except acute STEMI, is complex for the timing of invasive interventions and hard to identify. The approach and timing of the treatment are determined according to many factors, like the clinics of the patient, electrocardiographic variations, serum cardiac troponin, heart rate, creatinine, and heart failure symptoms. Vassalle et al. (29) determined that increased oxidative stress levels are associated with bad results in CAD patients while evaluating the relation of MACE and oxidative stress. They have stated that oxidative stress could be an important supplemental parameter to predict MACE in CAD patients. We also detected that oxidative stress markers might be convenient to show the severity of CAD in ACS patients as an easily measured, cheap laboratory parameter that yields early results.

Study limitations

Our study population was relatively small because of our exclusion criteria. We did not have clinical follow-up with these subjects. Future studies with a larger sample size are needed to evaluate the additive effect of oxidative stress as a prognostic indicator in CAD.

Conclusion

The results of our study make us think that oxidative stress markers can provide an opportunity to estimate the intensity of CAD biochemically. However, oxidative stress markers may not be considered useful biomarkers for the complexity of coronary lesions in ACS patients.

Conflict of interest: None declared.

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