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Plasma thiols and thiol-disulfide homeostasis in patients with isolated coronary artery ectasia

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ABSTRACT

Background and aims: Thiol/disulfide homeostasis has an important role in the antioxidant defense system. Oxidative stress may contribute to the pathogenesis of coronary artery ectasia. The aim of this study was to evaluate plasma thiol levels and thiol/disulfide homeostasis in patients with isolated coronary artery ectasia.

Methods: Forty-one patients with isolated coronary artery ectasia and 72 patients with normal coronary arteries were included in the study. Markis classification and number of ectatic coronary arteries were recorded. Plasma total thiol levels, native thiol levels and disulfide levels were measured. Thiol/disulfide homeostasis was appraised by calculating thiol/disulfide ratio.

Results: Plasma native thiol levels were significantly lower (336.9 (252.9–374.1) *vs.* 353.1 (327.0–380.0), $p = 0.041$) and disulfide levels were significantly higher (18.9 ± 6.3 *vs.* 16.6 ± 3.4, $p = 0.014$) in patients with coronary artery ectasia than control patients. Both native thiol/disulfide and total thiol/disulfide ratio was significantly lower in the coronary artery ectasia group ($p < 0.001$). Multivariate logistic regression analysis revealed that native thiol levels, disulfide levels and native thiol/disulfide ratio were independently associated with the presence of coronary artery ectasia. Thiol/disulfide ratio was not different according to number of ectatic coronary arteries and there was no association between thiol/disulfide ratio and Markis classification.

Conclusions: Plasma thiol/disulfide homeostasis is altered in patients with coronary artery ectasia.

1. Introduction

Oxidative stress plays a role in the pathogenesis of many diseases and previous studies showed the association between oxidative stress and various circumstances such as atherosclerosis, neurodegenerative diseases and malignancies [1–3]. Plasma thiols are a class of organic sulfur derivatives and they constitute an important part of the antioxidant defense system. In addition to their antioxidant role, they participate in several processes such as signaling, catalysis, metal complexing and structural stabilization. In the human body, they are present as large molecular weight protein thiols and low molecular weight free thiols. Glutathione, thioredoxin and glutaredoxin are known as endogenous biothiols. Reactive oxygen substrates can damage DNA, lipids and proteins and under oxidative stress, sulfhydryl compounds of thiols form disulfide bounds, when interacting with an oxidant molecule, and neutralize the molecule to a less toxic form. This homeostasis between thiols and disulfide bounds can represent the oxidative status of the organism [4–8].

Coronary artery ectasia (CAE) is defined as the localized or diffuse coronary artery segment dilation of 1.5 times or higher compared to the adjacent normal coronary segment [9]. The mechanism of coronary artery ectasia (CAE) is still unclear. Some congenital disorders such as polycystic kidney disease and Ehler Danlos syndrome are associated with CAE [10,11]. In addition, CAE may be diagnosed in patients with several types of vasculitis or connective tissue disorders [12,13]. However, most of the patients with CAE do not have any congenital disorder or any connective tissue disease. Vascular inflammation and destruction of the arterial media are at the center of the proposed mechanisms for CAE. This hypothesis is supported by studies demonstrating increased inflammatory marker levels in CAE patients [14]. Oxidative stress

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triggers vascular inflammation [15] and imbalance between antioxidant and pro-oxidant status may play a role in the development of CAE. The prognostic significance and morbidity of CAE are still not definitely exerted. Patients with CAE may be asymptomatic but these patients may also complain about angina, may have abnormal cardiovascular stress test or may be presented with non-ST elevational myocardial infarction, ST elevational myocardial infarction and sudden cardiac death [16].

As we mentioned above, patients with CAE may have an increased cardiovascular risk, therefore, understanding the underlying mechanism of CAE is important to reduce the cardiovascular risk in these patients. It seems that the most important mechanism for CAE is vascular inflammation and destruction of the arterial media [14,17]. It is known that oxidative stress triggers vascular inflammation [15]. Endogenous thiols and thiol-disulfide homeostasis has an important role in the antioxidant balance and the association between CAE and thiol-disulfide homeostasis is still unknown. We aimed to evaluate the plasma thiols and thiol-disulfide homeostasis in patients with isolated CAE.

2. Materials and methods

This cross-sectional study was approved by the local ethical committee of Ankara Numune Education and Research Hospital and informed consents were obtained from all patients before involving them into the study.

2.1. Study population

Individuals who accepted to participate were recruited between January 2015 and September 2015. Patients with isolated CAE and patients with normal coronary arteries as control group were enrolled into the study. Coronary angiographies were evaluated by at least two independent cardiology specialists. The location of ectatic coronary segment, number of coronary vessels with ectasia and Markis classifications [18] were recorded. Patients with any renal, hepatic and inflammatory disease, patients with a final diagnosis of vasculitis, patients with active infection, heart failure, acute coronary syndrome and obstructive coronary lesions were excluded from the study. In our study population, there was no patient with genetic connective tissue disorder having CAE.

2.2. Blood sample collection and thiol-disulfide homeostasis determination

All blood samples were obtained following the angiography. The samples were centrifuged at 1500*g* for 10 min. Plasma was stored at −80 °C and all samples were processed simultaneously. Serum lipid parameters, creatinine levels, hemogram parameters were obtained from local laboratory records. Thiol-disulfide homeostasis was determined as described previously [19].

2.3. Statistical analysis

Normality of distribution of the continuous variables was tested using Kolmogorov-Smirnov test. Results are presented as mean ± standard deviation for normally distributed variables and as median (interquartile range 25–75) for abnormally distributed variables. Statistical comparisons between continuous variables in CAE and control groups were performed with independent samples *t*-test or Mann-Whitney *U* test, in accordance with normality test results. Statistical comparisons of categorical variables were performed using Chi-square test. For more than two independent groups, statistical comparisons of median values were performed using Kruskall-Wallis H test. The dependent variable of the study was the presence of isolated CAE. Independent variables were age,

Table 1
Baseline characteristics of the study patients.

	Control group (n = 72)	CAE (n = 41)	*p* Value
Age, years (mean ± SD)	54 ± 11	58 ± 11	0.069
Gender, male, n(%)	33(45.8)	30(73.2)	0.005
Hypertension, n(%)	23(31.9)	18(43.9)	0.204
Smoking, n(%)	8(11.1)	3(7.3)	0.513
Diabetes mellitus, n(%)	18(25.4)	10(24.4)	0.910
Creatinine, μmol/L (mean ± SD)	76.9 ± 13.3	83.1 ± 18.6	0.089
Total cholesterol, mmol/L (mean ± SD)	5.2 ± 1.3	4.8 ± 1.1	0.128
HDL, mmol/L (mean ± SD)	1.3 ± 0.4	1.0 ± 0,2	0.002
LDL, mmol/L (mean ± SD)	3.4 ± 1.2	2.8 ± 0.9	0.024
Triglyceride, mmol/L, median (IQR)	1.3(0.8–2.0)	1.5(1.1–2.2)	0.181
Hemoglobin, gr/dl (mean ± SD)	14.1 ± 1.6	14.4 ± 1.7	0.448
Platelet count,*10^3 (mean ± SD)	247 ± 49	227 ± 61	0.101
WBC count, (mean ± SD)	7400 ± 1800	7900 ± 1900	0.217
Neutrophil count (mean ± SD)	4500 ± 1600	5000 ± 1500	0.131
Lymphocyte count, median (IQR)	2100(1650–2500)	2100(1500–2300)	0.526
Monocyte count, median (IQR)	500(400–600)	540(500–700)	0.182
CRP, nmol/L	1.90(0.95–2.85)	1.92(1.52–5.14)	0.224
Total thiol, μmol/L, median (IQR)	380.8(362.7–414.6)	366.2(287.4–406.7)	0.123
Native thiol, μmol/L, median (IQR)	353.1(327.0–380.1)	336.9(252.9–374.1)	0.041
Disulfide, μmol/L (mean ± SD)	16.6 ± 3.4	18.9 ± 6.3	0.014
Native thiol/disulfide ratio, median (IQR)	21.1(18.3–24.7)	15.3(13.51–22.4)	<0.001
Total thiol/disulfide ratio, median (IQR)	23.1(20.3–26.7)	17.4(15.5–24.4)	<0.001
Number of ectatic coronary arteries			
1	–	26(63.4)	
2	–	6(14.6)	–
3	–	9(22.0)	
CAE distribution			
LAD	–	23(56.1)	
CX	–	17(41.4)	–
RCA	–	25(60.9)	

CAE: coronary artery ectasia, CRP: C reactive protein, CX: circumflex, HDL: high density lipoprotein, LAD: left anterior descending, LDL: low density lipoprotein, RCA: right coronary artery, WBC: white blood cell.