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Increased Plasma Levels of Thioredoxin in Patients with Coronary Spastic Angina

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ABSTRACT

To determine whether plasma levels of thioredoxin are associated with coronary spasm, we measured the plasma levels of thioredoxin in 170 patients who had <25% organic stenosis in coronary arteriography. According to the results of cardiac catheterization, we divided the patients into two groups: a coronary spastic angina group (n = 84) and a chest pain syndrome group (n = 86). The plasma levels of thioredoxin were significantly higher in the coronary spastic angina group than in the chest pain syndrome group (40.7 ± 4.1 versus 18.2 ± 1.1 ng/ml, $p < 0.0001$). Furthermore, the increased plasma levels of thioredoxin were associated with high disease activity indicated by the frequency of angina attacks ($p = 0.0004$). In multiple logistic regression analysis, the higher levels of thioredoxin [relative risk 14.8, 95% confidence interval (5.13–42.9), $p < 0.0001$] and current smoking [relative risk 3.39, 95% confidence interval (1.31–8.75), p= 0 .012] were significant and independent variables associated with coronary spasm. We demonstrated that the plasma levels of thioredoxin were increased in the coronary spastic angina group, and increased levels of thioredoxin were associated with high disease activity. The plasma levels of thioredoxin and current smoking were risk factors for coronary spastic angina, and they were independent from other traditional risk factors. *Antioxid. Redox Signal.* 6, 75–80.

INTRODUCTION

OXIDATIVE STRESS plays an important role in the mechanism(s) of endothelial dysfunction in cardiovascular diseases (2, 3). Previous studies showed that the impairment of endothelium-dependent vasodilation as well as the hypercontractile response of smooth muscle in coronary arteries may play an important role in the genesis of coronary spasm (6, 25). Either vitamin C or E improves the impairment of response to acetylcholine in epicardial coronary arteries of patients with coronary spastic angina (7, 10). It has been shown that the plasma levels of vitamin E, natural antioxidants, were decreased in patients with coronary spastic angina (9).

Adult T cell leukemia-derived factor (ADF) was originally defined as an interleukin-2 receptor α-chain inducer in human lymphotronic virus-1-transformed cells and is identical to thioredoxin (20, 23). Thioredoxin is a small multifunctional protein that contains a redox-active dithiol/disulfide in the active site and shows a variety of biological functions, including cytoprotection against oxidative stress (13). Pevious studies have shown that plasma/serum levels of thioredoxin are elevated under oxidative stress-associated disorders such as viral infections and ischemia–reperfusion (12, 14). Recently, thioredoxin in human plasma has been measured quantitatively by a sandwich enzyme-linked immunosorbent assay (ELISA) (12, 14). Plasma concentration of thioredoxin

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may be one of the good markers for the host response against oxidative stress. Until now, there has been no investigation on the relation between plasma thioredoxin and coronary spasm, to our best knowledge. The aim of the present study was to examine the relation between (a) oxidative stress and coronary spasm and (b) oxidative stress and disease activity of coronary spasm.

MATERIALS AND METHODS

Study protocol

This study enrolled 203 consecutive patients who had <25% organic stenosis in coronary arteriography. They underwent elective and diagnostic cardiac catheterization for chest pain at rest in Kumamoto University Hospital. Thirty-three patients were excluded because they had one of the following exclusion criteria: myocardial infarction, major surgery and trauma, or serious infectious disease within the previous 4 weeks; malignancies; or chronic inflammatory disease. Ultimately, 170 (84%) of the 203 patients were included in this study. We divided the 170 patients into a coronary spastic angina group and a chest pain syndrome group. The study included 84 patients with coronary spastic angina and normal coronary angiograms who underwent cardiac catheterization in our hospital. The patients with coronary spastic angina fulfilled all of the following inclusion criteria: (a) spontaneous anginal attacks associated with ST-segment elevation or depression on the electrocardiogram at rest; and (b) coronary artery spasm (total or subtotal occlusion) demonstrated angiographically by intracoronary infusion of acetylcholine (26). We defined the remaining 86 patients in whom coronary spasm was not provoked in any coronary artery as chest pain syndrome patients. The clinical characteristics of the study patients are shown in Table 1. Both groups did not have peripheral artery disease. All medications except sublingual nitroglycerin were withdrawn at least 3 days before the coronary arteriography. The study patients had not taken any pharmacological doses of antioxidants for at least 1 month before the study. None of the patients had myocardial infarction, congestive heart failure, cardiomyopathy, valvular heart disease, or any other serious disease. Written informed consent was obtained from all patients before the study. The study was in agreement with guidelines approved by the ethics committee of our institution.

Cardiac catheterization

Coronary arteriography was performed in all patients using the Judkins technique in the morning when the patients were fasting. Incremental doses of acetylcholine (20, 50, and 100 μg/min for 1 min) were infused into the left and right coronary arteries separately until coronary spasm was induced or the maximal dose was reached as previously reported (4). This method allows us to provoke spasm in both coronary arteries separately and to safely evaluate the presence of multivessel spasm. The sensitivity and specificity of this method for provoking coronary spasm have been validated (16). A coronary angiogram was obtained at the end of each infusion. Coronary spasm was defined as a total or subtotal occlusion of the epicardial coronary arteries associated with chest pain and ischemic ST-segment changes (26). We divided the patients with coronary spastic angina into a high disease activity group and a low disease activity group. Patients who had spontaneous attacks associated with ST-segment elevation or depression on the electrocardiogram at least three times a week were defined as high disease activity. The other patients with coronary spastic angina were defined as the low disease activity group.

Blood sampling

The peripheral blood samples were drawn into a tube containing sodium citrate via venipuncture in the morning in a fasting state after admission. All subjects lay recumbent, and a 21-gauge needle was inserted into an antecubital vein. The samples for the thioredoxin assay were immediately cen-

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY GROUPS

Characteristics	*Coronary spastic angina (n = 84)*	*Chest pain syndrome (n = 86)*
Age (years)		
Mean	63 ± 1	62 ± 1
Range	41–81	38–80
Sex (n), man/woman (man%)	54/30 (64)	46/40 (53)
Coronary risk factors		
Hypertension (BP ≥ 140/90 mm Hg, *n*, %)	23 (27)	30 (35)
Diabetes mellitus (*n*, %)	18 (21)	19 (22)
Obesity (BMI ≥ 25 kg/m_2, *n*, %)	19 (23)	19 (22)
Current smoking (*n*, %)	29 (35)*	17 (20)
Serum total cholesterol (mg/ml)	188 ± 4	189 ± 4
Serum LDL cholesterol (mg/ml)	114 ± 3	114 ± 3
Serum HDL cholesterol (mg/ml)	51 ± 2	55 ± 2
Serum triglyceride (mg/ml)	130 ± 8	135 ± 8

Values are expressed as means ± SEM. BMI, body mass index; BP, blood pressure.
*$p < 0.05$ versus chest pain syndrome.

trifuged (4°C, 3,000 rpm, 15 min) and stored at −80°C until analyzed.

Plasma thioredoxin assay

Two different kinds of anti-human thioredoxin murine monoclonal antibodies (ADF-11 and ADF-21) and a sandwich ELISA for human thioredoxin were provided by Redox Bioscience, Inc. (Kyoto, Japan) and used as previously described (12–14). As a standard, serial dilutions of 5–320 ng/ml of human thioredoxin were used. Data were analyzed using Version 2.3 of SOFT max software by matching with four parameter logit–log transformation of standard human thioredoxin.

Statistical analysis

All data are expressed as mean values ± SEM. Because the levels of plasma thioredoxin were not distributed normally, nonparametric analyses were used. To examine the differences in thioredoxin level as an independent risk factor between the coronary spastic angina and chest pain syndrome groups, multiple logistic regression was conducted using the following factors as categorical covariates: high levels of thioredoxin (≥3;32.9 ng/ml, which was the 75th percentile of the distribution of the plasma thioredoxin levels in all the patients) in this study, age (≥70), sex (man%), current smoker (defined as smoking at least 10 cigarettes per day for ≥10 years), hypertension (>140/90 mm Hg or requiring antihypertensive medication), diabetes mellitus [according to ADA report (24)], hypercholesterolemia (>220 mg/dl or the use of lipid-lowering medications), high low-density lipoprotein (LDL) cholesterol (>130 mg/dl), low high-density lipoprotein (HDL) cholesterol (<35 mg/dl), and hypertriglyceridemia (>150 mg/dl). The mean values of continuous variables with a normal distribution and frequency between the two groups were obtained by unpaired t test and χ^2 analysis. Probability levels of <0.05 were considered significant.

RESULTS

Characteristics of the study population

The clinical characteristics of the study population are shown in Table 1. There were no significant differences between the coronary spastic angina and chest pain syndrome groups in terms of age, sex, hypertension, diabetes mellitus, obesity, serum total cholesterol, serum HDL cholesterol, serum LDL cholesterol, and serum triglyceride levels. The prevalence of cigarette smoking was significantly higher in the coronary spastic angina group than in the chest pain syndrome group ($p < 0.05$). However, there was no significant difference between the levels of thioredoxin and current smoking ($p = 0.12$, $r^2 = 0.015$).

Plasma levels of thioredoxin

The plasma levels of thioredoxin were significantly higher in the coronary spastic angina group than in the chest pain syndrome group (40.7 ± 4.1 versus 18.2 ± 1.1 ng/ml, $p < 0.0001$) (Fig. 1). In the coronary spastic angina group, the plasma levels of thioredoxin were significantly higher in the high disease activity group than in the low disease activity group (62.9 ± 10.6 versus 31.4 ± 3.5 ng/ml, $p = 0.0004$) (Fig. 2). Furthermore, we examined whether medical treatment reduces the plasma levels of thioredoxin in 12 of 25 patients with high disease activity. As a result, the levels of thioredoxin were decreased with improvement of disease activity by drug therapy (44.3 ± 9.2 versus 19.5 ± 3.1 ng/ml, $p < 0.01$) (Fig. 3). We also examined whether vitamin E, an antioxidant, affects the levels of thioredoxin in 15 patients with stable coronary spastic angina. As a result, the levels of thioredoxin were significantly decreased by vitamin E (26.6 ± 2.8 versus 13.4 ± 2.4 ng/ml, $p < 0.01$).

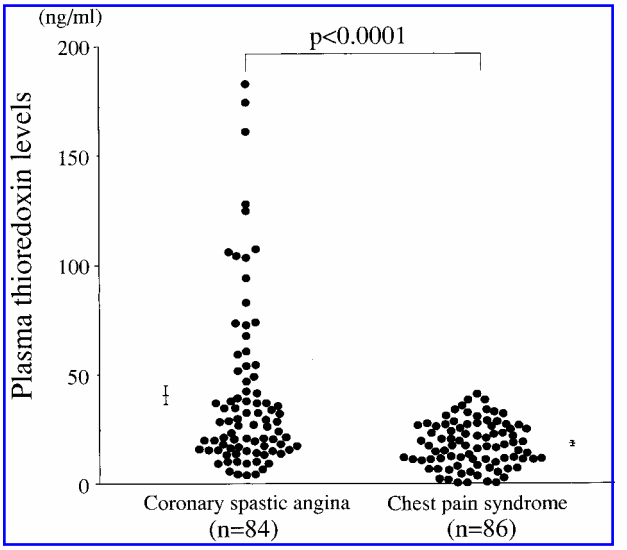

FIG. 1. Comparison of plasma thioredoxin levels between coronary spastic angina and chest pain syndrome groups.

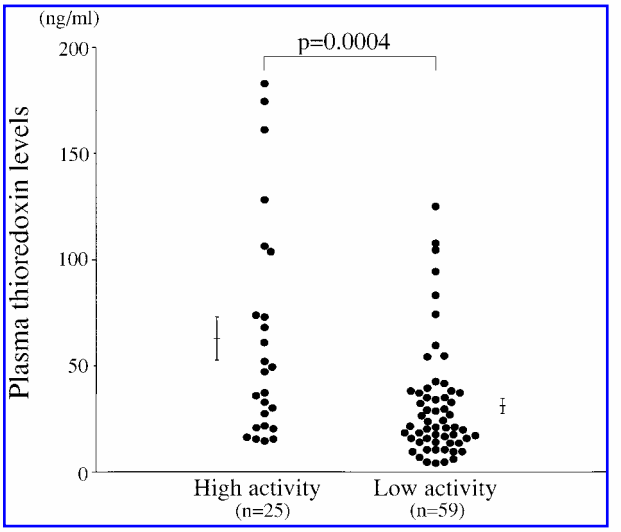

FIG. 2. In patients with coronary spastic angina, comparison of plasma thioredoxin levels between high disease activity and low disease activity groups.

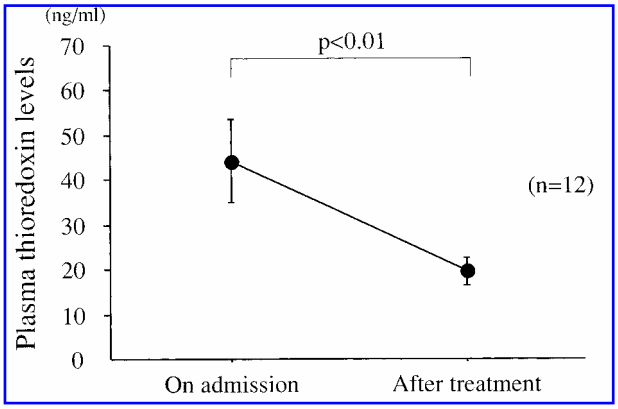

FIG. 3. Plasma thioredoxin levels in the coronary spastic angina group on admission and after treatment.

Comparison of thioredoxin levels between coronary spastic angina and chest pain syndrome groups

In multiple logistic regression analysis, the levels of thioredoxin and current smoking were independent variables that were significantly different between the coronary spastic angina and chest pain syndrome groups (Table 2).

DISCUSSION

The present study showed that plasma levels of thioredoxin were significantly increased in patients with coronary spastic angina as compared with those with chest pain syndrome. We also demonstrated that in patients with coronary spastic angina, the plasma levels of thioredoxin were more increased in the high disease activity group than in the low disease activity group. Further, the levels of thioredoxin were decreased with improvement of disease activity by drug therapy. These findings may indicate that oxidative stress is greater when disease activity is high in patients with coronary spastic angina. The multivariate logistic regression analysis showed that the higher levels of thioredoxin were a significant and independent risk factor for coronary spastic angina.

In the current study, the precise mechanisms of the increased oxidative stress in patients with coronary spastic angina were not determined. It is known that plasma levels of thioredoxin are elevated under oxidative stress-associated disorders such as viral infections, ischemia–reperfusion, and heart failure (5, 12, 14). Therefore, the increased thioredoxin levels might be the effect of the repetitive ischemia–reperfusion by coronary spasm. It is possible that increased plasma thioredoxin levels are not the cause of coronary spastic angina, but the result. Previous studies showed that the impairment of endothelium-dependent vasodilation as well as the hypercontractile response of smooth muscle in coronary arteries may play an important role in the genesis of coronary spasm (6, 25). Both the lack of nitric oxide activity (6, 15) and the mutation of nitric oxide synthase gene have been reported as a cause of coronary spasm (15, 27). In addition, increased reactive oxygen species inactivate endothelial nitric oxide and lead to endothelial dysfunction (11, 23). On the other hand, a previous study showed evidence for superoxide-dependent coronary spasm (8).

Cigarette smoking is a major risk factor for coronary spasm (19, 21), and it has been shown that cigarette smoke contains large amounts of free radicals such as superoxide anions and hydroxyl radicals (1, 18), which could degrade endothelium-derived nitric oxide (11, 17). Cigarette smoking would, therefore, be expected to predispose patients to coronary spasm. In the present study, the prevalence rate of current smoking was significantly higher in the coronary spastic angina group than in the chest pain syndrome group.

In the present study, the levels of thioredoxin were decreased by the antioxidant vitamin E. We have previously shown that, in patients with coronary spastic angina, the administration of vitamin E as a dietary supplement decreased oxidative stress and improved endothelial function, with resulting decrease in the number of anginal attacks (10). Thus, the administration of antioxidants might be one of the therapeutic options for treating patients with coronary spastic angina. A sensitive indicator of oxidative stress such as thioredoxin could be a useful marker for antioxidative treatment.

TABLE 2. MULTIPLE LOGISTIC REGRESSION ANALYSIS: VARIABLES DIFFERING BETWEEN THE CORONARY SPASTIC ANGINA AND CHEST PAIN SYNDROME GROUPS

Variable	*Relative risk*	*95% CI*	p *value*
Plasma thioredoxin > 32.9 ng/ml	14.8	5.13–42.9	<0.0001
Current smoking	3.39	1.31–8.75	0.012
Age ≥ 70 years	0.64	0.29–1.41	0.27
Man	0.92	0.39–2.20	0.86
Diabetes mellitus	1.04	0.41–2.62	0.93
Hypertension	0.61	0.27–1.36	0.23
Total cholesterol > 220 mg/dl	1.97	0.57–6.80	0.29
LDL cholesterol > 130 mg/dl	0.84	0.29–2.40	0.74
HDL cholesterol < 35 mg/dl	0.24	0.04–1.59	0.14
Triglyceride > 150 mg/dl	1.87	0.75–4.63	0.18

CI, confidence interval.

Conclusions

We showed that plasma levels of thioredoxin were increased in the coronary spastic angina group and higher thioredoxin levels were associated with high disease activity indicated by the frequency of anginal attacks. Furthermore, the plasma levels of thioredoxin and current smoking were risk factors for coronary spastic angina, and they were independent from other traditional risk factors.

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ABBREVIATIONS

ADF, adult T cell leukemia-derived factor; ELISA, enzyme-linked immunosorbent assay; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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