Original Article

The Relationship between Tenascin-C Levels and the Complexity of Coronary Lesion after Myocardial Infarction

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***Aim*: The increase of tenascin-C levels after myocardial infarction has been demonstrated by previous studies. The relationship between tenascin-C and the grade of stenosis in the infarct-related coronary artery was indeterminate. The aim of this study was to evaluate the relationship between tenascin-C levels and total occlusion after acute myocardial infarction.**

***Method*: Fifty-nine patients with subacute anterior myocardial infarction were divided into two groups according to their having a totally or subtotally occluded left anterior desending artery. Plasma tenascin-C, troponin I, CK-MB, uric acid, mean platelet volume, and lipid profile levels were also measured.**

***Results*: The history of the smoking rate, hypertension and diabetes mellitus were similar in both groups. Hemoglobin, mean platelet volume, serum creatinine, CK-MB, troponin I, serum lipid profile and uric acid levels were similar in the two groups. The CRP and tenascin-C levels were significantly higher in the total occlusion group. Tenascin-C levels were highest in patients with proximal LAD total occlusion and lowest in patients with subtotal LAD occlusion. The tenascin-C levels were correlated with the grade of stenosis ($r=0.602$, $p<0.001$).**

***Conclusion*: This study demonstrates that higher tenascin-C levels were related with the total occlusion and inflammation after MI.**

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Key words; Tenascin-C, Total occlusion, Acute myocardial infarction

Introduction

Myocardial infarction (MI) is a very common and serious disease that causes mortality. Infarct size is a major predictor of mortality and left ventricular functions following MI. The patency of an infarct-related artery was independently associated with better LV function, electric stability and mortality with a smaller infarct[1]; therefore, it is very important to determine the degree of the lesion in the infarct-related artery after MI.

Tenascin-C is an extracellular matrix glycoprotein that reorganizes the cell shape of the heart during cardiac repair after acute MI[2]. It also has multiple functions, such as cell proliferation[3], migration[4], differentiation[5] and apoptosis[6]. Tenascin-C is also expressed in various pathological conditions, including human coronary atherosclerotic plaque[7], abdominal aorta aneurysm[8], MI[2, 9], myocarditis[10], malignant tumours[11-14] and pulmonary hypertension[15, 16]. Tenascin-C levels increase after cardiac injury and inflammation. Tenascin-C is also detected in the marginal zone between the infarct area and the intact area after myocardial infarct[8, 17] and it is thought that tenascin-C is a useful marker to predict left ventricular remodeling and prognosis after acute myocardial infarction[18]. C-reactive protein (CRP) is a marker commonly used to show an acute inflammatory response and it increases after cardiac injury and inflammation. It was also used to demonstrate ventricular remodeling after acute MI[19].

The purpose of this study was to evaluate the val-

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ue of tenascin-C levels to determine the totally occluded infarct-related artery in a coronary angiography after acute MI.

Methods

Study population

We prospectively investigated 59 patients with subacute anterior myocardial infarction between June and December 2009. The exclusion criteria included the following; a history of previous pulmonary hypertension, undergoing any primary reperfusion therapy, coronary artery disease, heart failure, multi-vessel disease in coronary artery and cardiomyopathy. The study was approved by the the local ethics committee. All patients were informed about the study, and their written consent was obtained.

Coronary Angiography

A conventional coronary angiography was performed with Philips Integris 5000 equipment (Philips Medical Systems, Best, Netherlands) in patients within 24 hours after admission. After obtaining images by standard approaches, each angiogram was interpreted by two independent cardiologists. The coronary lesions were classified as either total occlusion or subtotal occlusion in the infarct-related left anterior desending artery (LAD). The criterion for total occlusion was absent antegrade flow, defined as a thrombolysis in myocardial infarction (TIMI) flow grade of 0 and subtotal occlusion was defined as a critical stenosis (60-99%) in infarct-related LAD. Each of the coronary segments was graded according to its most severe diameter reduction as follows: 60-69% stenosis, 70-79% stenosis, 80-89% stenosis, 90-99% stenosis and 100% occlusion with no antegrade flow.

Fifty-nine patients were divided into two groups according to the angiographic properties of their coronary angiographies. The total occlusion LAD group consisted of 37 patients with total occlusion in the infarct-related LAD and the subtotal occlusion LAD group consisted of 22 patients with subtotal occlusion in the infarct-related LAD.

Biochemical analysis

Blood samples were obtained within 24 hours of presentation. Measurements were performed with an Olympus Chemistry analyzer AU640-type 643-03 device (Manufactory Mishima Olympus Co. Ltd., Shizuoka, Japan). Blood samples for tenascin-C (ELISA Kit for Human Tenascin-Uscn Life Science Inc.) were obtained, centrifuged, and then stored at −70℃. Tenascin-C levels were analyzed after the blood samples of all study patients were obtained. Troponin I (Access® 2 Immunoassay System from Beckman Coulter, Inc.) levels were also measured in all patients. Mean platelet volume (MPV) and hemoglobin (Hb) were measured from Tripotassium EDTA-based anticoagulated blood samples and assessed by a *Sysmex* K-1000 autoanalyzer within 30 minutes of sampling. CRP was measured using a BN2 model nephlometer.

Statistical analysis

Continuous variables were given as the mean ± SD; categorical variables were defined as percentages. Comparisons between total and subtotal occlusion groups were carried out using an independent sample *t* test. Comparisons between the proximal LAD total occlusion group, middle + distal LAD total lesion group and subtotal LAD lesion group were carried out using one-way ANOVA and Tukey's post-hoc test. Correlation analyses were performed using the Pearson coefficient of correlation. SPSS 15.0 software was used for basic statistical analysis (Version 15; SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was accepted as statistically significant.

Results

The demographic characteristics of patients are summarized in **Table 1**. The mean age was 63 ± 11 years in the total occlusion group and 59 ± 12 years in the subtotally occluded group ($p = 0.3$). In the total occlusion LAD group; 10 of the 37 patients were female and in the subtotally occluded LAD group; 7 of the 22 patients were female (27 %, 31 %, respectively, $p = 0.6$). The average time of admission after MI was five days in all study patients. All of the blood samples were taken immediately after admission on an average of five days after the onset of symptoms.

The rate of smoking, history of hypertension and diabetes mellitus were similar in both groups. In the biochemical examination, hemoglobin, mean platelet volume, serum creatinine, creatine kinase isoenzyme MB mass (CK-MB), troponin I, serum lipid profile and uric acid levels were similar in the two groups (**Table 1**). The CRP levels were significantly higher in the totally occluded group than in the subtotal occlusion group (**Table 1**). The tenascin-C levels were also significantly higher in the total occlusion group (**Fig. 1**); however there was no significant correlation between CRP levels and tenascin-C levels.

When the patients were divided into three groups, proximal LAD total occlusion group, middle + distal LAD total lesion group and subtotal LAD lesion group; the tenascin-C levels were significantly

Table 1. Demographic properties of patients in two groups

	Total Occlusion Group (n = 37)	Subtotal Occlusion Group (n = 22)	P value
Age	63.1 ± 11.2	59.9 ± 12.8	0.3
Diabetes Mellitus (n, %)	12 (32 %)	5 (23 %)	0.3
Hypertension (n, %)	16 (43 %)	7 (32%)	0.2
Smoking (n, %)	22 (59 %)	13 (59 %)	0.5
Creatinine (mg/dL)	1.1 ± 0.3	0.9 ± 0.1	0.1
Hemoglobin (mg/dL)	14.2 ± 1.6	14.0 ± 1.3	0.6
Mean platelet volume (fl)	10.3 ± 0.8	10.5 ± 0.8	0.3
Troponin I (ng/mL)	2.6, 0.04- 99	11.6, 0.05- 99	0.5
Total cholesterol (mg/dL)	193 ± 53	187 ± 41	0.6
Triglyceride (mg/dL)	151 ± 97	145 ± 76	0.7
LDL-C (mg/dL)	116 ± 37	120 ± 34	0.6
HDL-C (mg/dL)	40 ± 10	37 ± 9	0.3
CK-MB(μg/L)	79 ± 65	104 ± 93	0.2
Uric acid (mg/dL)	6.2 ± 1.6	5.8 ± 1.9	0.4
CRP (mg/L, median, min-max)	17.6, 3- 171	14.7, 3- 96	0.02

Data are expressed as the mean ± SD or median, min-max. $P < 0.05$ was accepted as statistically significant. LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol, CK-MB = creatine kinase isoenzyme MB mass, CRP = C-reactive protein

Table 2. Comparison of Tenascin-C levels according to infarct-related lesion localization

	Proximal LAD Total Lesion (n = 22)	Middle + Distal LAD Total Lesion (n = 15)	Subtotal LAD Lesion (n = 22)	P value
Level of Tenascin-C (ng/mL)	25.3 ± 8.2	24.2 ± 11.4	17.6 ± 7.9	0.01

Data are expressed as the mean ± SD. $P < 0.05$ was accepted as statistically significant. LAD = left anterior desending artery

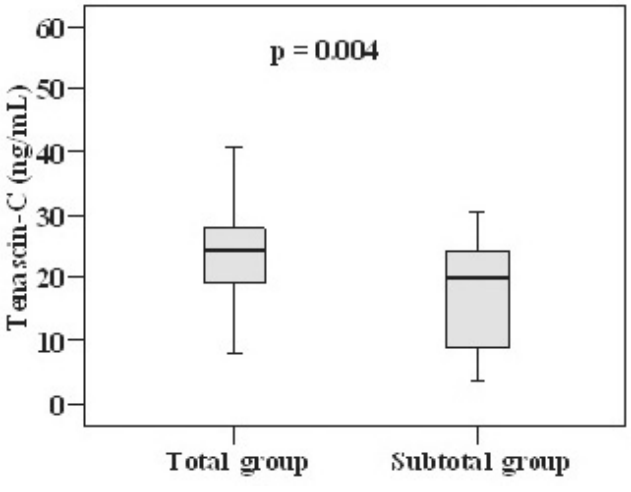

Fig. 1. Comparison of the tenascin-C levels in two groups (p = 0.004).

lower in the subtotal LAD lesion group (**Table 2**). The highest tenascin-C levels were seen in the proximal LAD total occlusion group (**Table 2**). In post-hoc analysis; there was no significant difference in tenascin-C levels between the proximal LAD total occlusion group and middle + distal LAD total lesion group (25.3 ± 8.2 and 24.2 ± 11.4, respectively, p = 0.9). The tenascin-C levels were significantly higher in the proximal LAD total occlusion group than the subtotal LAD lesion group (25.3 ± 8.2 and 17.6 ± 7.9, respectively, p = 0.01). The tenascin-C levels were higher in the middle + distal LAD total occlusion group than the subtotal LAD lesion group (24.2 ± 11.4 and 17.6 ± 7.9, respectively, p = 0.08).

Tenascin-C levels also did not correlate with the mean platelet volume and uric acid levels. There was a significant correlation between the tenascin-C levels and grade of stenosis (r = 0.602, $p < 0.001$).

Discussion

The total occlusion of an infarct-related coronary artery after MI can cause many complications, such as left ventricular (LV) remodeling, LV dysfunction, heart failure and electrical instability. The purpose of the recanalization of the infarct-related artery (IRA) after MI is to prevent these pathological conditions. Hence, the grade of occlusion in IRA should be shown in all of the patients with acute coronary syndromes. The expression of tenascin-C increases the early phase of fibrosis and cardiac repair after cardiac injury[20]. It has also been observed in human coronary atherosclerotic plaque[7] but the relation between higher tenascin-C levels and the coronary lesion's anatomy was indeterminate.

This is the first study demonstrating higher tenascin-C levels in total occlusion IRA rather than in subtotal occlusion IRA after MI.

Sato *et al*. studied tenascin-C levels in acute MI patients. They showed that tenascin-C levels were elevated after the onset of symptoms, peaked at 5 days, and remained at high levels at 28 days after onset. They found significantly higher levels in acute MI patients than old MI patients and healthy subjects. Tenascin-C levels were also significantly higher in the LV remodeling group[18]. Our study patients' mean tenascin-C measure time was five days after the onset of ischemic symptoms and we found higher levels in the patients in the total occlusion group than subtotal occlusion group. In our opinion, totally occluded LAD causes more remodeling than subtotally occluded LAD because the totally occluded IRA was more associated with LV remodeling than subtotally occluded IRA, which had TIMI-3 flow and a less necrotic area after MI; therefore, it might be one of the mechanisms for the higher tenascin-C levels in totally occluded LAD.

Synthesis of tenascin-C by cardiac fibroblasts is stimulated by myocardial injury and inflammation after MI; the infarct size is also one of the major determining factors for higher tenascin-C levels[18]. This may explain the higher levels of tenascin-C in totally occluded IRA after MI.

CRP and carotis intima media thickness were related with the pathogenesis of cardiovascular disease and predicted coronary artery disease and cerebrovascular events. Inflammation markers such as CRP and fibrinogen have been independently associated with the incidence of coronary events[21]. It was also shown that high CRP levels were related with patients who have cardiovascular disease[22, 23]. Likewise, in our study, CRP levels were significantly higher in the totally occluded LAD group who had higher risk lesions than the other group. Similarly, higher tenascin-C levels were seen in the totally occluded LAD group; therefore, we believe that elevated tenascin-C levels were related with high-risk lesions such as total occlusion. According to these results, it was shown that tenascin-C plays an important role in predicting the complexity of coronary lesions and inflammation.

The limited number of patients is the most important limitation of our study. The lack of evaluation of the infarct size and ventricular remodeling with echocardiography, scintigraphy or ventriculography was also an important limitation. In our opinion, elevated tenascin-C levels are associated with total coronary occlusion and should be reanalyzed after recanalization of the occluded IRA and compared with unopened occluded IRA.

Conclusion

This study demonstrated that higher tenascin-C levels were seen in patients with a totally occluded infarct-related artery after MI and that elevated tenascin-C levels after MI may be an indicator of total occlusion and inflammation.

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