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Role of Tenascin-C as a Predictor of Left Ventricular Remodeling after Streptokinase in Patients with Acute Myocardial Infarction

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Abstract

We investigated clinical implications of serum tenascin-C (TN-C) levels in patients with acute myocardial infarction (AMI) treated with thrombolytic therapy Serum TN-C levels were measured by ELISA in 60 cases presented with acute STEMI and 20 normal controls. The mean serum TN-C level of AMI patients on admission (57.5 ng/ml) was significantly higher than that of controls (57.49 ± 19.89 ng/ml *vs.* 34 ± 3.02 ng/ml; p=0.0001), follow-up examination (mean: 6 months) revealed that 17 of 60 AMI (28%) patients showed left ventricular (LV) remodeling (20% end-diastolic volume increase), and in 6 (10%), major adverse cardiac events (MACE) were detected. By receiver-operating characteristic (ROC) analysis, TN-C levels clearly discriminated prediction of LV remodeling and MACE compared with other variables including creatine kinase-MB, and LV function. Diabetes and TN-C were correlated with MACE in our study. The findings suggest that serum TN-C levels might be useful in predicting LV remodeling and prognosis after AMI.

Keywords: Remodeling; Creatine kinase; Thrombolytic therapy; Streptokinase; Myocardial infarction

Introduction

Left Ventricular regional motion dysfunction defined as segmental impairment in systolic wall thickening develops in 25% of patients after Myocardial infarction and predicts adverse events [1]. LV remodeling is a major predictor of morbidity and mortality for overt congestive heart failure (CHF) and life-threatening arrhythmias [2]. It occurs in an appreciable proportion of patients with AMI successfully treated with primary percutaneous transluminal coronary angioplasty (PTCA) despite sustained patency of the infarct-related artery (IRA) and preservation of regional and global LV functions [3].

It has been reported that infarct size, anterior infarct location, perfusion status of the culprit lesion, and CHF on admission are major predictors of LV dilation. Moreover; several factors including B-type natriuretic peptide (BNP), cardiac troponin I, and high-sensitivity C-reactive protein, have been also examined as potential predicting biomarkers of LV remodeling [3].

Tenascin-C (TN-C) is an extracellular matrix protein specifically expressed at high levels during embryonic development, wound healing, and cancer invasion and involved in regulation of cell behavior during tissue remodeling in various tissues [4]. In the heart, TN-C is normally expressed in early-stage embryos, playing important roles in development of the myocardium, valves, and coronary vessels [5].

TN-C is sparsely detected in the normal adult myocardium, but reappears when the heart remodels its structure in response to pathologic insults, such as acute myocardial infarction (MI), myocarditis, hibernation, ischemia-reperfusion, hypertensive cardiac fibrosis, chronic cardiac rejection and some cases of dilated cardiomyopathy (DCM). Under these pathological conditions; myocardial cell death takes place, caused by destructive stress triggers inflammation, which is an important process for proper tissue repair [6]. Although the expression of TN-C in the vascular system appears a little more complex compared with that in the heart, the expression of TN-C in the normal vascular wall is generally low. High tissue levels of TN-C have been reported within a variety of vascular diseases, including intimal hyperplasia, atherosclerosis, pulmonary artery hypertension and abdominal aortic aneurysm [7]. Accumulating evidence suggests that TN-C may enhance inflammatory responses. For example, TN-C may activate innate immunity as DAMP (damage-associated molecular patterns) to stimulate the production of the pro-inflammatory cytokines in macrophages and fibroblasts via a TLR-4-mediated signaling pathway. It also modulates adaptive immunity via the Integrin α9 pathway and cytokine up regulation with the activation of NF-κ β [7].

Patients and Methods

This study included 60 patients with AMI and was successfully treated by thrombolytic therapy (42 men and18 women, mean age 56.2 ± 6.2 years), admitted to Minia University Hospital between January 2014 and January 2015. Twenty age and gender-matched, apparently healthy volunteers (14 men and 6 women, mean age 53 ± 7.4 years with normal resting Echocardiography study) were included as controls.

Inclusion criteria

Chest pain >30 minutes in duration and present within 12 hours after onset of symptoms, ST segment elevation at electrocardiogram (ECG) with cut-points consistent with ST elevation MI (STEMI) diagnosis according to ESC guidelines 2012 [≥ 0.1 mV in two contiguous ECG leads at J point in all leads other than leads V2-V3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 years; ≥ 0.25 mV in men <40 years, or ≥ 0.15 mV in women and these changes in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)], elevated Troponin I and/or CK mb within 12 hours of chest pain, evidence of successful thrombolysis according to ESC guidelines 2012

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[Relief of chest pain, more than 50% ST segment resolution at ECG obtained within 60-90 minutes after thrombolytic therapy, occurrence of reperfusion arrhythmia as accelerated idio-ventrcular rhythm (AIVR) is specific for reperfusion. Primary ventricular fibrillation (VF) is now thought to be reperfusion related].

Echocardiographic assessment

Transthoracic two-dimensional echocardiograms were obtained from all patients within 1st week after MI and for controls using GE VIVID 3, USA.

Standard parasternal and apical views were obtained in left lateral decubitus. The LV dimensions, end diastolic volume (EDV) and end systolic volume (ESV) were measured.

Follow up studies were done for all patients by the 6th month after AMI. The LV remodeling was defined as „An increase in EDV at six months after infarction by ≥ 20% in comparison with the baseline measurement in individual patient" according to Bolognese et al. [8].

Biochemical analysis

Serum Troponin I level and CKmb were measured within 12 hours of chest pain for all patients. Serum TN-C in patients with acute MI is significantly elevated, peaks at day 5, and then gradually decreases [7] so serum level of Tenascin C was done after 5-7 days from admission with acute myocardial infarction. Blood samples were centrifuged at 15,000 g for 15 min, and resulting supernatants were stored until analysis. Serum levels of TN-C with the large subunit containing the C domain of FNIII repeats were determined using an ELISA kit with two monoclonal antibodies, 4F10TT and 19C4MS (IBL, Gunma, Japan).

Follow-up

Follow up of those patients was in the special outpatient clinic for the cardiovascular disease at Mina University hospital by the 6th month from the onset of AMI for major cardiac events (MACE) as cardiac death, CHF and acute coronary syndrome (ACS) and for hospitalization.

The Follow up Echocardiographic study for detecting occurrence of LV remodeling was done at same visit for all patients.

Statistical analysis

Two-tailed tests were used throughout and statistical significance was set at the conventional level of less than 0.05. The range, means and standard deviation (SD) were calculated for interval and ordinary variables, frequencies and percentages for categorical variables. Multiple comparisons were carried out by Student's t-test, and Chi-Squared (χ^2) test was used for non-parametric measure of statistical independence of the categories of two variables measured on the nominal or dichotomous scale. The Bivariate Correlations were measured using Pearson's correlation coefficient as a measure of linear association. A backward/stepwise multiple linear regression models were calculated with the occurrence of LV remodeling as the dependent variable. The Receiver Operating Characteristic (ROC) and Area under curve (AUC) presented along with its 95% confidence interval (CI) were obtained, in order to measure the overall performance of a diagnostic test, and the operating point, at which best sensitivity and specificity were obtained.

Results

There was no statistically significant difference between the patients and control regarding age, gender and EDV, while TN-C was significantly higher in post AMI patients (57.5 ± 19.9 ng/ml versus 34.1 ± 3.2 ng/ml, p<0.0001) (Table 1).

Parameters		Patients (no= 60)	Controls (no= 20)	P value
Age	mean ± SD	56.2 ± 6.2	53 ± 7.4	NS
Gender	Male	42 (70%)	14 (70%)	NS
	Female	18 (30)	6 (30%)	
HTN	Positive	24 (40%)	7 (35%)	NS
DM	Positive	9 (15%)	4 (20)	NS
Smoking	Positive	31 (52%)	10 (50%)	NS
Tenascin-C	mean ± SD	57.5 ± 19.9	34.1 ± 3.2	**<0.0001**
EDV_1	mean ± SD	92.7 ± 14.9	91.2 ± 9.9	0.05

Student t-test, Chi-square test, Significant P value<0.05
SD: Standard Deviation; HTN: Hypertension; DM: Diabetes Mellitus; EDV_1: Basic Left Ventricle End-Diastolic Volume, NS: Non Significant

Table 1: Comparison between patients and controls.

The end-diastolic and end-systolic volumes (EDV, ESV and ejection fraction) were measured, and LV remodeling was defined by ≥ 20% increase in EDV at 6 months after MI in comparison to basic measurements [8]. Patients were classified into two groups according to the occurrence of LV remodeling in follow up Echocardiography (Mean follow-up EDV of remodeling group was 126.4 ± 27.6 ml versus 93.9 ± 15.4 ml for non-remodeling group, p=0.02). There was no statistically significant difference between both groups regarding age, sex, hypertension, smoking, infarct site, troponin I level, basic EDV and MACE. Remodeling group included more diabetic patient, higher CKmb level. TN-C was significantly higher in remodeling than non-remodeling group (80.3 ± 19.9 ng/ml versus 47.6 ± 9.5 ng/ml, p=0.002) (Table 2).

Serum TN-C, CKmb and DM were positively correlated with LV remodeling, while higher serum TN-C levels and DM were correlated with occurrence of more MACE (Table 3).

Multivariate regression analysis for the risk factors correlated with LV remodeling showed that TN-C was the most independent predictor for LV remodeling (Table 4).

ROC analysis of TN-C as a predictor for LV remodeling revealed AUC of 0.872, with cutoff level of ≥ 68.9 ng/ml can predict LV remodeling with 81% sensitivity and 95% specificity (Figure 1).

Discussion

The principal findings of this study were:

1) High serum TN-C levels in patients post AMI, even those who were successfully treated with thrombolytic therapy. 2) High serum TN-C levels can independently predict occurrence of LV remodeling in patients post AMI. 3) DM and high serum TN-C level are correlated with higher incidence of MACE and LV remodeling post AMI. Thus, serum TN-C levels in acute stages following AMI might be a predictive biomarker of LV remodeling and prognosis during the recovery phase.

Several prior animal studies had reported the association of TN-C with LV remodeling, as Nishioka et al. who reported that TN-C may aggravate LV remodeling and systolic dysfunction after MI in mice [9]. Another study by Taki et al. demonstrated the dynamic expression of TN-C after myocardial ischemia and reperfusion in rats assessed by anti-TN-C antibody imaging [10]. Also Yoshida et al. reported that TN-C modulates adhesion of cardiomyocytes to extracellular matrix during tissue remodeling after MI. Moreover, they reported that it is a useful marker for disease activity in myocarditis [11,12].

Parameters		Remodeling group (n=16)	Non-remodeling group (n=42)	P value
Age	Mean ± SD	56.9 ± 6.8	55.6 ± 6.1	0.74
Sex	Male	12 (75%)	29 (69%)	0.46
	Female	4 (25%)	13 (31%)	
HTN	Positive	8 (50%)	15 (36%)	0.24
DM	Positive	6 (38%)	1 (5%)	**0.001**
Smoking	Positive	10 (62%)	20 (48%)	0.24
CKmb	mean ± SD	328.6 ± 128.3	205.6 ± 88.1	**0.09**
Troponin ng/ml	mean ± SD	2.3 ± 0.9	1.7 ± 0.8	0.97
Tenascin-C	mean ± SD	80.3 ± 19.9	47.6 ± 9.5	**0.002**
EDV_1	mean ± SD	93.8 ± 15.1	92.3 ± 15.4	0.75
EDV_2	mean ± SD	126.4 ± 27.6	93.9 ± 15.4	**0.02**
MACE	Mean ± SD	2 (12.5%)	2 (5%)	0.3

Student t-test, Chi-square test, Significant P value<0.05, SD: Standard Deviation; HTN: Hypertension; DM: Diabetes Mellitus; CKmb: Creatine Kinase (mb) subtype; EDV_1: Basic Left Ventricle End-Diastolic Volume; EDV_2: Follow-up Left Ventricle End-Diastolic Volume; MACE: Major Adverse Cardiac Events.

Table 2: Comparison between Remodeling and Non-remodeling patients groups.

Parameters		Remodeling	MACE
Age	r	0.091	0.19
	P value	0.499	0.147
HTN	r	0.131	0.181
	P value	0.329	0.165
DM	r	0.482**	0.482**
	P value	**0**	**0**
Smoking	r	0.133	-0.122
	P value	0.319	0.352
Infract site	r	-0.068	0.212
	P value	0.614	0.104
Troponin I	r	0.297	-0.139-
	P value	0.111	0.446
CKmb	r	0.487**	0.239
	P value	**0**	0.066
Tenascin-C	r	0.487**	0.271*
	P value	**0**	**0.036**
EDV_1	r	0.044	-0.051
	P value	0.74	0.7
Remodeling	r	-	0.136
	P value	-	0.307
MACE	r	0.136	-
	P value	0.307	-

HTN: Hypertension; DM: Diabetes Mellitus; CKmb: Creatine Kinase (mb) subtype; EDV_1: Basic Left Ventricle End-Diastolic Volume; MACE: Major Adverse Cardiac Events.

Table 3: Correlation between Remodeling and MACE with other parameters.

Variable	B	SE	P value
DM	0.083	0.154	0.59
CKmb	0.099	0.149	0.51
Tenascin-C	0.017	0.002	**<0.0001**

B: Estimated Coefficient; SE: Standard Error; CK¬mb: Creatine Kinase (mb) subtype

Table 4: Multivariate regression analysis for risk factors using LV remodeling as a dependent variable.

In agreement with our results; previous studies had similarly reported an increased serum TN-C level in post AMI and with LV remodeling.

Imanaka-Yoshida et al. observations suggested that TN-C can be a key molecule to explore and diagnose cardiac remodeling, and might be a potential therapeutic target to control the balance of beneficial and undesirable cellular response [13].

Sato et al. reported that high serum levels of TN-C are associated with increased incidence of LV remodeling and MACE after AMI, and serum TN-C levels might be useful in predicting LV remodeling and prognosis after AMI. The study included 105 patients post AMI who had successful primary percutaneous intervention (PCI), with samples for TN-C were withdrawn at 5^{th} to 7^{th} day of admission Sato et al. Furthermore, they demonstrated that TN-C level is potentially used for early risk stratification after AMI and with prognostic value on long-term outcomes after AMI at study on 239 patients with serum TN-C measured on 5^{th} day after admission and on follow up [14].

Moreover, Ozlem et al. found higher TN-C levels in AMI patients with poor myocardial reperfusion after primary PCI to infarct-related artery (IRA) compared to those who achieved normal reperfusion after that intervention, the study included 58 patients [15].

Another study by Gaber et al. showed that serum TN-C might be a novel marker reflecting structural remodeling in the myocardium following MI. The study included 45 cases; 15 patients with AMI, 15 patients with heart failure on top of MI and 15 normal controls. Venous blood samples were taken on day of admission [16].

On the other hand, best of our knowledge that is no study in the literature had investigated the relationship between TN-C and

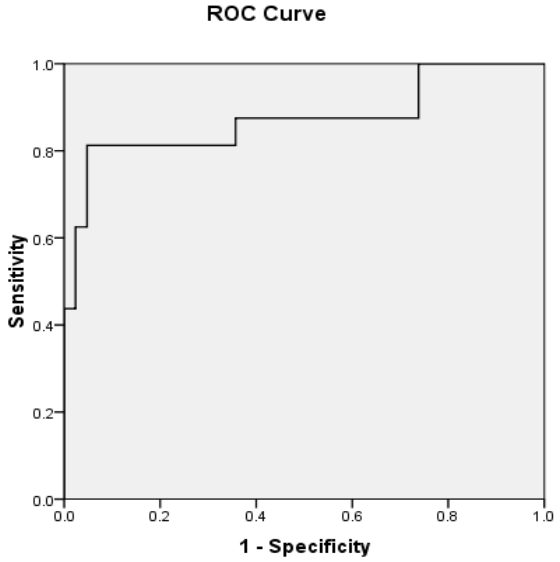

Figure 1: ROC curve of TN-C as predictor for of LV remodeling.

myocardial reperfusion after thrombolysis by streptokinase in AMI. Çelik reported that TN-C level was related with the coronary lesion complexity after MI, and its level was higher in patients with total IRA occlusion. The study included 59 patients with AMI, who were divided into two groups according to having a totally or sub totally occluded anterior descending artery [17].

Wallner et al. had investigated the pattern of expression of TN-C in human coronary atherosclerotic plaques, and showed that all atherosclerotic plaques with an organized lipid core or ruptured intimal surface strongly expressed TN-C, and its expression correlated with the infiltration of macrophages [18].

Moreover, Kenji et al. discovered that circulating TN-C level is associated with coronary plaque instability in patients with acute coronary syndrome. Immunohistochemical techniques were used to analyze the expression of TN-C in coronary atherectomy specimens obtained from 51 patients; with stable angina pectoris or with acute coronary syndrome (ACS) [19].

An interesting study by Sakamoto et al. reported that TN-C expression and accumulation in arterial mural injury contributed to both plaque inflammation and rupture. The study included 52 patients with ACS underwent emergency PCI, 66 patients with stable angina pectoris, blood samples were obtained from ascending aorta just prior to PCI, after coronary guide-wire crossing, intravascular ultrasonography (IVUS) was performed for assessment of plaque characterization. Based on IVUS findings, ACS patients subdivided into two groups according to presence or absence of ruptured plaque [20].

Another study by Minear et al. showed that TN-C is an important factor in the later stages of atherosclerotic plaque formation, because of its roles in promoting SMC migration and proliferation, and its replicated association with severe and advanced atherosclerotic and CAD phenotypes. The study investigated the differential expression of TN-C in atherosclerotic aortas compared to healthy aortas [21].

Furthermore, Schaff et al. discovered that thrombocytes interact with TN-C through von-Willebrand factor and the adhesion that occurs via that interaction subsequently triggers thrombocyte activation [22].

These data clearly reveal that TN-C is not only related to plaque instability but also to thrombogenicity after plaque rupture in ACS. This explains why patients with high level of TN-C level had LV remodeling in our study and other studies. The local inflammatory response in coronary artery after an acute coronary event as increased TN-C level in unstable plaque, systemic increase in TN-C level and inflammatory enzymes along with and TN-C mediated triggered thrombocyte activation and the increased thrombogenicity all adversely affect coronary microcirculation. Patients with poor coronary reperfusion despite recanalization of IRA with mechanical revascularization eventually suffer myocardial stunning, leading to a lack of expected recovery in left ventricular pump function.

Based on the results of our study and other previously reported studies we may suggest that; in patients with high TN-C levels, myocardial reperfusion may remain far from ideal even after successful thrombolysis or PCI. In this context, high TN-C can predict long-term outcomes like LV remodeling and poor prognosis.

Conclusion

However, despite the findings, the current study has some limitations. First, the sample size was relative small. Second, prognosis of our AMI patients received thrombolytic therapy, which is now inferior to primary PCI, which is recommended now. Also, there were short follow-up period of 6 months. Further large-scale prospective investigations and careful comparisons with other clinical parameters are therefore required to confirm the predictive ability of TN-C in LV remodeling and MACE.

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