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Serum S100A4 levels as a novel biomarker for detection of acute myocardial infarction

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Abstract. – OBJECTIVE: Myocardial infarction causes significant mortality and morbidity. Timely diagnosis allows clinicians to risk stratify their patients and select appropriate treatment. Biomarkers have been used to assist with timely diagnosis, while an increasing number of novel markers have been identified to predict outcome following an acute myocardial infarction or acute coronary syndrome. The objective of this study was to determine S100A4 expression in AMI and determine whether S100A4 could be a biomarker for detection of acute myocardial infarction (AMI).

PATIENTS AND METHODS: We measured circulating S100A4 levels in 173 patients (median age 58.3 years) who presented with first-time AMI 8 hours after the incident. The circulating S100A4 levels in 173 healthy volunteers (median age 57.3 years) was also measured. S100A4 was detected using enzyme immunoassay in both groups.

RESULTS: Serum S100A4 levels were significantly higher in patients with AMI [89.6 (4.3-214.6) pg/ml] compared to controls [11.8 (0-41.5) pg/ml] ($p < 0.001$). We found that a S100A4 level > 41.5 pg/ml had a Sensitivity 76.3% and specificity 87.5% for predicting AMI. S100A4 revealed the higher sensitivity for diagnosing AMI.

CONCLUSIONS: Elevated S100A4 in plasma may be a novel biomarker for early detection of AMI.

Key Words:
Acute myocardial infarction, Biomarker, S100A4.

Introduction

Acute myocardial infarction (AMI) represents a major health problem, because of the diminished flow of blood to the heart, leads to higher rates of mortality and morbidity[1]. Rapid diagnosis of AMI is critical for clinicians who could guarantee the immediate initiation of reperfusion therapy[2]. Thus, exploring novel biomarkers for AMI is essencial[3].

S100 proteins are calcium-binding proteins that generally exist as homo- or heterodimers within cells[4]. It has been reported to function as endogenous danger signals playing an active role in tissue inflammation and repair when released from necrotic cells[5]. S100A1 is the most abundant member of the calcium-binding S100 protein family in myocardial tissue. When released from damaged cardiomyocytes during myocardial infarction. Patients with AMI showed significantly increased S100A1 serum levels[6]. Expression of the S100 calcium-modulated protein family member S100A9 is also elevated in platelets from patients presenting with acute myocardial infarction (AMI) compared with those from patients with stable coronary artery disease[7]. Schiopu et al[8] has reported that elevated plasma levels of S100A8/A9 are associated with increased risk of future coronary events in healthy individuals and in myocardial infarction survivors. S100A8/A9 might represent a useful biomarker and therapeutic target in cardiovascular disease.

Recent reports[9-11] show that S100A4 are also present in various biological fluids including blood and the levels of S100A4 are linked to the diagnosis and prognosis for disease. We hypothesized that the S100A4 might release into the circulation during AMI and the elevated S100A4 in plasma from AMI patients could be potential biomarkers for the diagnosis of AMI.

Patients and Methods

Study Population

Our case-control study included 173 patients who presented with AMI for the first time and

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were assessed 4 hours after the incident. Controls consisted of 173 healthy individuals matched by the "frequency matching method" for age, sex, and body mass index (BMI). Cases presented with AMI from Jan 2011 through Oct 2013 was from the Department of internal medicine-cardiovascular, the Affiliated Hospital of Qingdao University, Qingdao, China and controls were randomly selected from participants of the center of physical examination of the Department of cardiology. Patients with inflammatory diseases, infectious diseases, renal or liver problems, diabetic patients, pregnancy and those with any history of myocardial infarction were excluded. The study was approved by the Ethical Committee of Department of Cardiology, the Affiliated Hospital of Qingdao University, Qingdao, China. All participants formally consented to participate in all stages of the study.

Anthropometric Measurements and Clinical Assessments

AMI was diagnosed based on elevation of myocardial necrotic markers in the serum and ST segment elevation on electrocardiogram[12]. BMI was calculated using the international standard equation (weight/height^2) and recorded as kg/m^2. Waist circumference was defined as the measurement around the narrowest diameter between the lower costal margin and iliac crest. Hip circumference was defined by measuring around the widest diameter over the greater trochanters. These findings were used to calculate the waist-to-hip ratio (WHR). Blood pressure was measured at least 10 minutes before blood sampling in both groups.

Laboratory Procedures

Both groups fast 10-12 hours, then the blood samples were collected. Samples were then centrifuged, coded and stored at –70°C until analyzed. Serum levels of high-density lipoprotein (HDL), total cholesterol (TCH), and low-density lipoprotein (LDL), and fasting blood sugar (FBS) were measured with enzymatic methods. A commercially available ELISA Kit was used to measure serum S100A4 levels. The average inter- and intra-assay coefficients of variation were < 10% for all assays.

Statistical Analysis

The results were represented as mean ± standard deviation and all statistical analyses were performed using the SPSS11.0 computer software (SPSS Inc., Chicago, IL, USA). Comparisons between S100A4 levels across different groups were performed using Mann Whitney-Wilcoxon test. Comparisons between means were performed by ANOVA or *t*-test where appropriate. For continuous variables not normally distributed, the variables are given as median (25^{th}-75^{th} percentile) and they were compared using the Mann-Whitney U-test. Survival curves were plotted using the Kaplan-Meier method. The difference in survival between groups was compared using the log-rank test. *p*-values less than 0.05 were considered statistically significant.

Results

S100A4 Levels in AMI and Healthy Individuals

A total of 173 patients with new onset AMI and no histories of any such prior incident as well as 173 healthy individuals (control group) were recruited for the study. In the healthy controls, the median serum levels of S100A4 were 11.8 (0-41.5) pg/ml, which was significantly lower than that in patients with AMI 89.6 (4.3-214.6) pg/ml (Figure 1, $p < 0.001$). The cut-off value was set at 41.5 pg/ml (75^{th} percentile of the S100A4 distribution in the controls). Higher

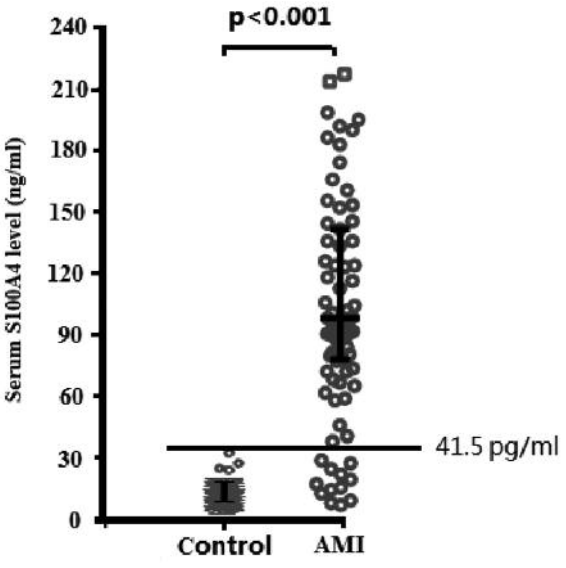

Figure 1. Comparison of serum S100A4 levels in healthy controls and patients with AMI. The horizontal line in each plot represents the cut-off value. $^*p < 0.001$.

Table I. Baseline characteristics of study subjects

Factor	AMI group	Control group	*p*-value
Number	173	173	--
Age (years)	58.3 ± 11.6	57.4 ± 10.8	0.62
Sex, male(%)	113(65.3%)	120(69.4%)	0.36
BMI (kg/m2)	23.4 ± 5.73	26.9 ± 5.18	0.82
Weight (kg)	68.3.8 ± 14.6	56.3 ± 17.2	0.29
Waist (cm)	100.4 ± 8.3	102.3 ± 9.3	0.84
SBP (mmHg)	139 ± 21.6	112.6 ± 17.4	0.000
DBP (mmHg)	79.5 ± 11.4	67.4 ± 12.4	0.000
Cholesterol (mg/dL)	201.6 ± 26.7	198.4 ± 22.8	0.71
TG (mg/dL)	130 ± 65.4	124.7 ± 50.3	0.72
HDL (mg/dL)	39.5 ± 8.37	32.4 ± 10.5	0.019
LDL (mg/dL)	119.3 ± 32.8	123.2 ± 23.4	0.36
FBS (mg/dL)	118.6 ± 17.3	95.4 ± 18.3	0.000
S100A4 (pg/mL)	89.6 (4.3–214.6)	11.8 (0–41.5)	0.002

Mean ± SD was reported: BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

serum S100A4 levels (≥ 41.5 pg/ml) were found in 72.8% (126/173) of patients with AMI, and 27.2% of patients (47/173) had levels lower than 41.5 pg/ml.

Correlationship of S100A4 with Other Clinical Characteristics

Clinical characteristics of the study groups are tabulated in Table I. There were no statistically differences regarding age, sex, BMI, weight, waist circumference, TCH, LDL, and TG levels between the study and control groups. However, mean SBP, DBP, and FBS was higher in the AMI group (all $p = 0.000$). HDL cholesterol was higher in controls compared to patients with ischemic heart disease. There were no differences in mean plasma S100A4 levels between males (5.1-216.7) pg/ml and females (4.6-212.4) pg/ml in the AMI group, for males (0-40.4) pg/ml versus females (0-41.9) pg/ml in the control group ($p > 0.05$ for all). As tabulated in Table II, no significant correlation was found between S100A4 serum levels and other factors in the study groups. Using multiple regression analysis, we also found no significant association between S100A4 levels and other factors.

Table II. Pearson correlation coefficients between serum S100A4 and other variables in study subjects.

Variables	Correlation coefficient	*p*-value
Waist	–0.138	0.32
SBP	0.135	0.23
DBP	0.063	0.472
Cholesterol	–0.047	0.217
TG	–0.014	0.803
HDL	–0.0625	0.536
LDL	–0.043	0.762
FBS	0.014	0.83

Specificity and Sensitivity of S100A4 to Detect AMI

The serum S100A4 level in AMI and S100A4 level in control was subjected to ROC curve analysis, and the results shown that the AUC (± SEM) was 0.764-0.9283, the sensitivity was 76.3% and specificity was 87.5% (Figure 2). Therefore, serum S100A4 level can be as the marker for the detection of AMI.

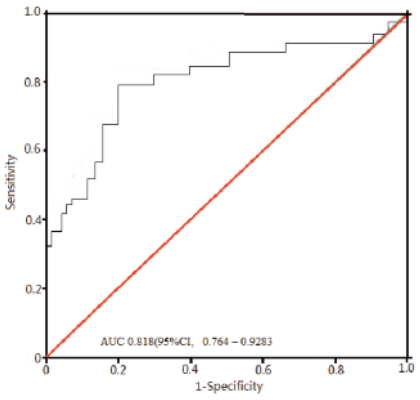

Figure 2. ROC curve used for the definition of the cut-off value of S100A4 that best characterizes AMI and control groups.

Discussion

Acute myocardial infarction (AMI) during the early postpartum period is rare but may be associated with poor maternal outcome[13]. The currently used cardiac-specific serum marker do not meet all the criteria for an "ideal" marker of AMI. No test is both highly sensitive and highly specific for acute infarction within 6 hours following the onset of chest pain, the timeframe of interest to most emergency physicians in making diagnostic and therapeutic decisions[14].

Elevation in CK-MB is a vital component of ultimate diagnosis of AMI, but levels of this marker are normal in one fourth to one half of patients with AMI at the time of ED presentation[15]. Although SBP, DBP, FBS, TCH, LDL, and TG levels were used, they have less sensitivity and specificity[16,17]. Xin et al[18] has reported elevated serum sPLA2-IIa was associated with an increased risk of mortality and readmission for HF. Li et al[19] has reported plasma and serum miRNAs may be as novel biomarkers for diagnosis and prognosis of AMI.

It has recently found expression of S100A4 mRNA is increased in rat models of cardiac hypertrophy[20], and S100A4 play a supportive role in injured hearts[9]. Cardiac levels of S100A4 protein was significantly increased after heart injury[9,20]. The cardiovascular effects of S100A4 could be able to counteract the pathophysiological mechanisms of ischemic heart disease.

Our study showed that serum S100A4 levels were significantly high in AMI patients compared to controls. Furthermore, a S100A4 level > 41.5 pg/ml had a sensitivity of 76.3% and a specificity of 87.5% for detecting individuals with AMI. We believe that S100A4 may be considered as a biomarker for predicting the probability of AMI in the future. Elevated S100A4 in AMI patients might be a protective mechanism. Our findings support existing literature regarding the role of S100A4 in the process of AMI.

In the present study, we did not find significant relation between S100A4 and other biochemical parameters. The case-control design limited our ability to infer a causal relationship between increased serum S100A4 levels and AMI.

Conclusions

This report has showed elevated S100A4 serum concentrations in Chinese patients with AMI. S100A4 may be considered as a biomarker for predicting the probability of AMI. However, a large-scale prospective cohort study is necessary to determine the potential casual relationship between S100A4 and AMI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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