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Association between the plasma levels of IMA and coronary atherosclerotic plaque burden and ischemic burden in early phase of non-ST-segment-elevation acute coronary syndromes

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Abstract. – OBJECTIVE: Ischemia-modified albumin (IMA), a novel biochemical marker, is known to reflect ischemia in early phases of acute coronary syndrome (ACS). In the present study, we evaluated the role of IMA on the prediction of coronary atherosclerotic plaque burden and ischemic burden in patients with non-ST-segment-elevation acute coronary syndromes (NSTEACS).

PATIENTS AND METHODS: Ninety-six consecutive NSTEACS patients presented within the first three hours of symptom onset were prospectively enrolled in this study. Blood samples were collected in the first 30 min of admission for IMA measurement. Serum levels of IMA were analyzed using the rapid and colorimetric method and reported in absorbance units (ABSU). Coronary plaque burden was assessed by using angiographic Gensini score (GS). In addition, patients were divided into large (LIBG) and small ischemic burden (SIBG) groups based on angiography findings.

RESULTS: Patients were dichotomized into two groups according to median GS as follows; with GS ≤ 44 and GS > 44, respectively. Mean IMA was significantly higher in GS > 44 group as compared to GS ≤ 44 group (0.746 ± 0.15 *vs.* 0.550 ± 0.12 ABSU, $p < 0.001$). The GS was positively correlated with the levels of IMA (r = 0.673, $p < 0.001$). IMA was significantly higher in LIBG as compared to SIBG (0.745 ± 0.16 *vs.* 0.570 ± 0.13 ABSU, $p < 0.001$).

CONCLUSIONS: IMA measurement in early phases of NSTEACS may give predictive information about ischemic burden and coronary atherosclerotic plaque burden; thus, may be useful in decision-making about treatment options in these patients.

Key Words:
Ischemia-modified albumin (IMA), Coronary artery disease, atherosclerosis, Ischemia, Risk assessment.

Introduction

Although therapeutic approach and optimal timing of cardiac catheterization in patients with ST-segment-elevation myocardial infarction (STEMI) have been precisely defined; they may vary depending on the patient's risk level in non-ST-segment-elevation acute coronary syndromes (NSTEACS). Currently, less aggressive medical treatment and conservative or delayed invasive approaches are recommended for patients with low risk. Whereas, rapid invasive approach and more potent antithrombotic therapies are proposed for patients with high-risk NSTEACS[1,2]. For this reason, ischemic risk assessment is crucial in patients with NSTEACS. Previous studies have indicated that increases in any biomarker that elevates before the biomarkers of necrosis (cardiac troponins I and T), may provide an earlier assessment of overall patient risk and aid in identifying patients with higher risk of adverse events[3]. Therefore, later researches are focused on the cardiac biomarkers that increase before the development

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of necrosis (inflammatory cytokines cells, acute phase reactants, myeloperoxidase, pregnancy-associated plasma protein-A, C-reactive protein, high-sensitivity cardiac troponin, heart-type fatty acid binding protein, etc.) in the prediction of the high-risk patients[4,5]. Ischemia-modified albumin (IMA) can detect ischemia within minutes before the development of necrosis and it has been accepted as a diagnostic biomarker by American Food and Drug Administration. Reactive oxygen radicals that appear during ischemia changes the N-terminal of the albumin and this results in the decrease of the binding ability of the albumin to nickel, cobalt and copper. Plasma levels of IMA with decreased cobalt binding capacity can be measured by albumin cobalt binding test (ACB)[6,7].

The aim of this study is to investigate the role of IMA in predicting coronary atherosclerotic plaque burden and ischemic burden in patients with ACS without persistent ST-segment elevation.

Patients and Methods

Between the January 2015 and November 2015, the study participants were prospectively enrolled from a total of 915 patients who were admitted to the emergency department with potential symptoms of the non-ST-segment-elevation acute coronary syndrome (NSTEACS) at the Ahi Evren Thoracic and Cardiovascular Centre. Of these patients, 819 of them were excluded from participation, mostly (565 patients) because they did not meet the inclusion criterion of acute coronary syndrome (ACS) symptoms within the 3 hours before presentation at the emergency department. Finally, the study population consisted of 96 patients with NSTEACS including 34 patients with unstable angina pectoris (USAP) and 62 patients with non-ST-segment-elevation myocardial infarction (NSTEMI). We excluded patients whose chest pains began more than 3 hours before, because that was reported the IMA to be positive within 6-10 min of ischemia, and remains so for up to 6 h[8,9]. In a later report, IMA normalized within 2.5 h following the primary percutaneous coronary intervention (PCI) in patients with STEMI[10]. Also, we included patients without any history of coronary artery disease, because patients with significant chronic stenosis of the coronary vessels are expected to have a higher content of collaterals and this can cause the low ischemia, low levels of IMA and underestimation of ischemic burden[11]. Cerebrovascular, peripheral vascular and end-stage renal disease, liver cirrhosis, acute infections, malignancies, systemic sclerosis, prostatic diseases and patients with hypo or hyperalbuminemia which are known factors that alter the levels of IMA were also excluded[12-17]. The patients were evaluated with detailed clinical backgrounds, medications, findings of physical examinations and smoking. NSTEMI and unstable angina pectoris (USAP) were diagnosed with characteristic chest pain that lasted for 20 minutes with or without associated ST-segment depression $\geq$ 0.1 mV and/or T-wave inversion in 2 contiguous leads on the electrocardiogram or no electrocardiographic abnormalities and presence or absence of increased levels of troponin. Hypertension diagnosis was made if the patient was on an antihypertensive medication or if the blood pressure measurements was >140 mmHg systolic, >90 mmHg diastolic, or both on examination. Diabetes mellitus was defined as fasting plasma glucose levels 126 mg/dl on multiple measurements or current use of anti-diabetic medications. Estimating glomerular filtration rate (GFR) was calculated by using Cockcroft-Gault (CG) formula[18]. The study protocol conforms to the principles of Declaration of Helsinki and is approved by local ethic committee. Informed consent of all the patients was obtained for participation in the study.

Blood Samples

Peripheral venous blood samples of patients were obtained from a cubital vein into blood heparinized tubes within one hour of admission, prior to coronary angiography and intervention. The plasma was separated from the cells by centrifugation at 3000 rpm for 10 min and stored at −80°C until the day of biochemical analysis.

Measurement of IMA

IMA level (reduced cobalt to albumin binding capacity) was analyzed using the rapid and colorimetric method developed by Bar-Or et al[6]. Two hundred microliter (μL) of patient serum was placed into glass tubes and 50 μL of 0.1% CoCl2+6H2O (Sigma) was added. After gentle shaking, the mixture was left undisturbed for 10 minutes to ensure sufficient cobalt albumin binding. Then, 50 μL of 1.5 mg/mL dithiothreitol (DTT) was added as a coloring agent. After 2 minutes, 1 mL of 0.9% NaCl was added to quench the reaction. A control sample was prepared for every sample. At the DTT addition stage, 50 μL of distilled water was used instead of 50 μL of 1.5 mg/mL DTT to obtain a control sample without DTT. Sample absorbencies were analyzed at 470 nm

using a spectrophotometer (Shimadzu UV1601; Tokyo, Japan). Color formation in specimens with DTT was compared with a color formation in the control tubes, and the results were expressed as absorbance units (ABSU).

Coronary Angiography (CAG) Assessments

The coronary atherosclerotic burden of patients was assessed by using the Gensini score[19] which grades the narrowing of the lumen of the coronary arteries as 1 for 1-25% narrowing, 2 for 26-50% narrowing, 4 for 51-75% narrowing, 8 for 76-90% narrowing, 16 for 91-99% narrowing and 32 for total occlusion. This score is then multiplied by a factor that takes into account the importance of the lesion's position in the coronary arterial tree, for example: 5 for the left main coronary artery, 2.5 for the proximal left anterior descending (LAD) coronary artery or proximal left circumflex (LCX) coronary artery, 1.5 for the mid-region of LAD, and 1 for the distal LAD or mid-distal region of the LCX. The Gensini Score was expressed as the total of the scores for all coronary arteries. The median Gensini Score of the study population was calculated. Patients were dichotomized into two groups according to median Gensini score. In addition, patients were separated into 2 groups according to their ischemic burden; those with large ischemic burden (LIBG) – left main disease, 3-vessel disease, and 2 vessel disease with significant disorder of proximal left anterior descending artery or small ischemic burden (SIBG) – 2-vessel disease without significant disorder of the proximal left anterior descending artery or single-vessel disease and non-significant irregularities[20]. Significant stenosis on CAG was defined as ≥70% diameter stenosis, except for the left main artery, which was ≥50% diameter stenosis.

Statistical Analysis

Continuous variables were tested for normal distribution by the use of the Kolmogorov–Smirnov test. Variables not normally distributed were expressed as medians (interquartile ranges). Normally distributed continuous variables were expressed as mean values ± standard deviation. Categorical variables were summarized as frequency percentages and absolute numbers. Patients were dichotomized according to a median value of Gensini score. Likewise, patients were divided into 2 groups according to their angiographic ischemic burden. The means for normally distributed continuous variables were compared by independent-samples *t*-test. Skew-distributed continuous variables were compared using a Mann-Whitney U-test. Pearsons X^2-test was used to compare categorical variables. Correlation of Gensini score and angiographic ischemic burden with IMA were assessed by Spearman's correlation analysis. Receiver operating curve analysis (ROC) was used to calculate sensitivity and a specificity of IMA to predict the presence of intensive atherosclerotic plaque burden and large ischemic burden and to determine the best cut-off values. SPSS 17.0 software (SSPS Inc., Chicago, IL, USA) was used for all statistical calculations. p-values <0.05 were considered statistically significant.

Results

Baseline Characteristics

Of the ninety- six patients, 77 were male (80.2%) and the mean age was 64.8 ± 11.5 (Table I). Thirty-four (35.4%) patients had USAP, 62 (65.6%) patients had NSTEMI. The median Gensini score of the study population was 44. Patients

Table I. Comparison of the clinical, laboratory and angiographic characteristics of the study population (n = 96).

Age, years	64.8 ± 11.5
Male/female, n, (%)	77 (80.2) / 19 (19.8)
BMI, kg/m2	27.4 ± 4.3
Diabetes mellitus, n, (%)	21 (21.9)
Hypertension, n, (%)	81 (81)
Smokers, n, (%)	25 (26)
Drug Using	
Statins n, (%)	31 (32.3)
ACEI/ARB n, (%)	50 (52.1)
Beta blockers n, (%)	54 (56.3)
Nitrates n, (%)	9 (9.4)
LDL cholesterol (mg/dl)	124.2 ± 36.4
Urea (mg/dl)	43.2 ± 16.9
Creatinine (mg/dl)	0.97 ± 0.25
GFR (ml/min/1.73 m^2)	91.32 ± 35.2
Gensini score	47.9 ± 29.5
Syntax score	14.9 ± 10
Coronary vessel disease	
None	6 (6.3)
1 Coronary vessel disease, n, (%)	30 (31.3)
2 Coronary vessel disease, n, (%)	30 (31.3)
3 Coronary vessel disease, n, (%)	30 (31.3)
Left main coronary vessel disease, n, (%)	7 (7.3)
ACS	
NSTEMI, n, (%)	62 (64.6)
USAP, n, (%)	34 (35.4)

were dichotomized into two groups according to median Gensini score as follows; with Gensini score ≤ 44 and > 44, respectively. There were no significant differences among the groups with respect to sex, history of hypertension and diabetes mellitus, smoking, medications, body mass index (BMI), GFR and low-density lipoprotein levels (Table II). Likewise according to angiographic findings, patients were separated into two groups as large ischemic burden group (LIBG) and small ischemic burden group (SIBG). There were no significant differences among two ischemic burden groups with respect to baseline characteristics expect the age and smokers (Table II). Mean age and smokers were higher in LIBG.

Relationships Between Coronary Atherosclerotic Plaque Burden and IMA

Mean plasma levels of IMA were statically significantly higher in patients with Gensini score > 44 as compared to Gensini score ≤ 44 (0.746 ± 0.15 vs. 0.550 ± 0.12 ABSU, p <0.001; Table II, Figure 1A). In addition, there was a statistically significant positive correlation between the levels of IMA and Gensini score (r = 0.673, p < 0.001). In receiver operating curve (ROC) analysis, the cut-off value of plasma level of IMA to predict an intensive atherosclerotic plaque burden (GS > 44) with a sensitivity of 83% and a specificity of 77% was 0.606 ABSU (Area under curve, AUC = 0.853, 95% confidence interval, CI, 0.778-0.928, p < 0.001; Figure 2A).

Relationships Between Ischemic Burden and IMA

Mean plasma level of IMA was statistically significantly higher in LIBG than the SIBG (0.745 ± 0.16 vs. 0.570 ± 0.13 ABSU, p < 0.001; Table I, Figure 1 B). In receiver operating curve (ROC) analysis, the cut-off value of plasma level of IMA to predict a large ischemic burden with a sensitivity of 74% and a specificity of 72% was 0.622 ABSU (Area under curve, AUC = 0.805, 95% confidence interval, CI, 0.720-0.890, p < 0.001; Figure 2B).

Discussion

In the present study, we have demonstrated that increased plasma level of IMA in early phases of NSTEACS may reflect coronary atherosclerotic plaque burden and ischemic burden. There are conflicting results in studies about the assessment of the relation between IMA and CAD. In a study, Chek et al[21] investigated that

Table II. Comparison of clinical characteristics and serum levels of IMA according to the Gensini score (atherosclerotic plaque burden) and ischemic burden.

	GS ≤ 44 [n = 48]	GS > 44 [n = 48]	p	SIBG [n = 53]	LIBG [n = 43]	p
Age (years)	62.8 ± 12.4	66.8 ± 10.3	0.09	62.4 ± 12	67.7 ± 10.3	**0.022**
Male gender, n, (%)	39 (81.2)	38 (79.2)	1	43 (81.1)	34 (79.1)	0.8
BMI (kg/m2)	27.0 ± 3.8	27.8 ± 4.8	0.36	27.7 ± 4	27 ± 4.7	0.5
Diabetes mellitus, n, (%)	8 (16.7)	13 (27.1)	0.32	9 (17)	12 (27.9)	0.2
Hypertension, n, (%)	40 (83.3)	38 (79.2)	0.79	44 (83)	34 (79.1)	0.62
Smokers, n, (%)	10 (20.8)	15 (31.2)	0.35	9 (17)	16 (37.2)	**0.035**
Statin use, n, (%)	20 (41.7)	11 (22.9)	0.08	21 (39.6)	10 (23.3)	0.085
ACEI/ARB use, n, (%)	29 (60.4)	21 (43.8)	0.15	34 (64.2)	23 (53.5)	0.29
Beta blocker use, n, (%)	33 (68.8)	29 (62.5)	0.52	32 (60.4)	31 (72.1)	0.28
Nitrate use, n, (%)	7 (14.6)	2 (4.2)	0.15	5(9.4)	4(9.3)	0.42
LDL cholesterol (mg/dl)	122.6 ± 39.6	126.7 ± 32.6	0.59	124.1 ± 39.5	124.3 ± 32.7	0.97
Urea (mg/dl)	44.8 ± 18.8	41.6 ± 14.7	0.35	42.2 ± 17.1	44.5 ± 16.7	0.51
Creatinine (mg/dl)	0.98 ± 0.25	0.96 ± 0.25	0.72	0.96 ± 0.24	0.98 ± 0.25	0.74
GFR (ml/min/1.73 m2)	93.36 ± 38.2	89.3 ± 32.2	0.57	97 ± 38.3	84.3 ± 29.8	0.07
IMA (ABSU)	0.550 ± 0.12	0.746 ± 0.15	**<0.001***	0.570 ± 0.13	0.745 ± 0.16	**<0.001***

ABSU – Absorbance Unit; ACEI/ARB – angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI – body max index; GFR – Glomerular filtration rate; GS – Gensini score; IMA – Ischemia-modified albumin; LDL – low density lipoprotein; LIBG – Large ischemic burden group; SIBG – Small ischemic burden group; SS – Syntax score. * Statistically significant.

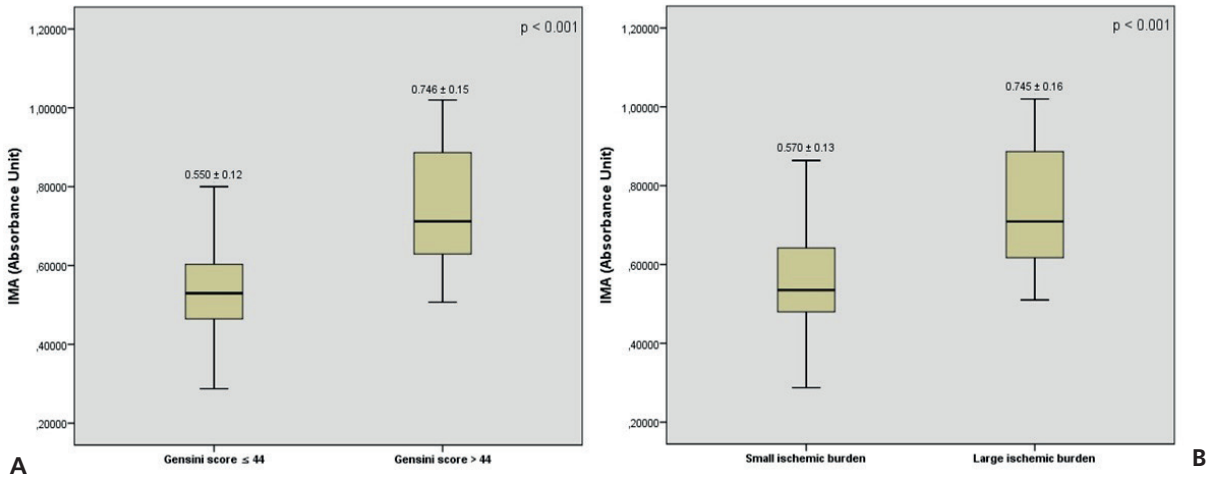

Figure 1. Relationships between the serum levels of IMA and Gensini score ***(A)*** and ischemic burden ***(B)***.

the role of the IMA for demonstration of the extends of the ischemia was searched in patients with STMI and they have reported that IMA has no value for the prediction of the extent of the ischemia. On the other hand, in this study, IMA was compared with necrosis markers such as cTn, CK-MB and ejection fraction and no association was found and the authors concluded that there was no relationship. However, since IMA is a marker of ischemia rather than myocardial cell damage, we have looked for the angiographic coronary atherosclerotic and ischemic burden in our study. In addition, as it was mentioned before in a study, IMA was normalized within 2.5 h following the primary percutaneous coronary intervention (PCI) in patients with STEMI[10]. In Chek et al[21] study, the time period between the beginning of the chest pain and referral to the hospital is relatively longer which was varied from 1.5 to 24 hours. Although patients were grouped according to time for the referral and there was no difference in between the groups, IMA values would be similar in patients with high ische-

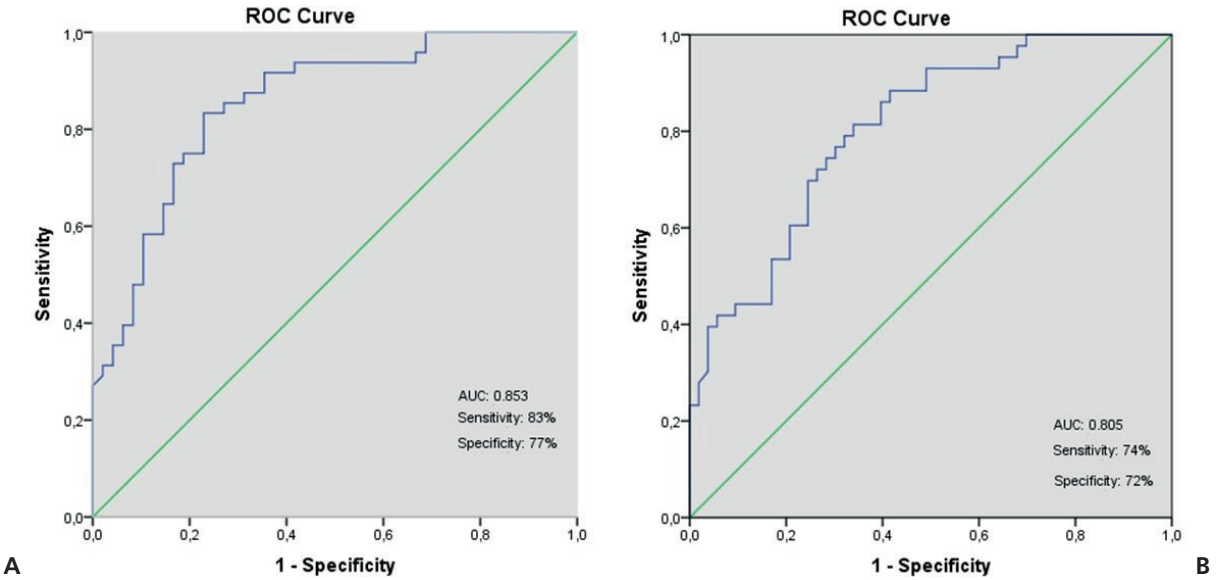

Figure 2. Receiver operating curve (ROC) analysis of plasma level of IMA for predicting intensive atherosclerotic plaque burden (A) and large ischemic burden (B). AUC, area under curve.

mic burden with long referral period and low ischemic burden with short referral time. For this reason, in our study we only included the patients who were referred within 3 hours of the beginning of the pain. IMA represents the in vivo modification of human serum albumin (HSA) N-terminus end by reactive oxygen species (ROS) and the concentration of serum IMA has been proposed as a biomarker in clinical conditions related to ischemia associated with oxidative stress, such as cardiac ischemia[22,23]. In our previous study[24], we investigated that relationship between oxidative stress markers (total oxidative status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI)) and the intensity of coronary artery disease in patients with ACS. We demonstrated that TOS and OSI values were significantly higher in the intensive CAD group and there was a significant positive correlation between Gensini score and oxidative stress markers (TOS and OSI). Similar to these studies, we found a significant positive correlation between coronary atherosclerotic plaque burden and plasma levels of IMA. Another purpose of our study was to identify the patients with high risk according to the plasma levels of IMA, who needs rapid invasive approach and more potent antithrombotic therapies. Our findings indicated that increased plasma level of IMA in early phases of NSTE-ACS was significantly and independently associated with an intensive coronary atherosclerotic plaque burden and a large ischemic burden. Van Belle et al[25] have investigated the plasma levels of IMA in patients with ACS including STEMI and NSTEMI. They demonstrated that serum levels of IMA measured within 24 hours of hospital admission is a strong predictor of cardiac outcome during the first year and may help to identify patients requiring more aggressive medical management following discharge from the hospital. Huang et al[26] investigated the association of 3 coronary scores with major adverse cardiovascular events (MACE) in patients with ACS. Their results suggest that the Gensini score provides a more valuable prognostic information on cardiovascular risk than either the Leaman et al[27] or American College of Cardiology/American Heart Association (ACC/AHA)[28-30] scores in patients with ACS. Also, the correlation between the severity of coronary artery lesions and Gensini score had been demonstrated in other current studies[31,32]. Therefore, we used the Gensini score in our work.

Our study has some limitations. Firstly, our study population was relatively small because of our exclusion criteria. Moreover, we did not have clinical follow-ups with these subjects. Future investigations with a larger sample size are needed to evaluate the IMA measurement for risk stratification of patients presented with ACS.

Conclusions

IMA measurement in early phases of NSTE-ACS may give predictive information about the ischemic burden and coronary atherosclerotic plaque burden; thus, may be useful in decision-making about treatment options in these patients.

Conflict of interest

The authors declare no conflicts of interest.

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