Original Article

Serum Chitotriosidase Activity in Acute Coronary Syndrome

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***Aim*: Inflammation is a critical participant in mediating all stages of cardiovascular disease. Studies related with chitotriosidase that was recently found to be relevant to arterial inflammation. In this study we evaluated activity of serum chitotriosidase in acute coronary syndrome patients and its relationship with cardiovascular events, cardiac enzymes and inflammatory indicators.**

***Methods*: We prospectively analyzed consecutive 30 patients with ST-segment elevation myocardial infarction, 30 patients with non ST-segment elevation myocardial infarction, 30 patients with unstable angina pectroris who were admitted to our intensive care unit and 30 healthy people (average age 56.86 ± 10.44 years, 81 male) between Jaunary and June 2010. Details of baseline clinical characteristics, biochemical values, receiving treatment and basal ECG findings were recorded. Data of patients with coronary angiography were evaluated.**

***Results*: Cut off value of chitotriosidase was calculated 82.00 mmol · ml-1 · h-1, with 83 percent sensitivity and 72 percent spesificity. The activity of chitotriosidase in acute coronary syndrome group was 88.85 ± 23.08 mmol · ml-1 · h-1, where as the control group was 68.47 ± 28.44 mmol · ml-1 · h-1, respectively $p=0.001$).The highest activity of chitotriosidase (96.11 ± 19.77 mmol · ml-1 · h-1) was found in ST-segment elevation myocardial infarction group and the minimal activity of chitotriosidase was in the control group (68.47 ± 28.44 mmol · ml-1 · h-1) ($p=0.001$). The activity of chitotriosidase in ST-segment elevation myocardial infarction and non ST-segment elevation myocardial infarction groups were significantly higher than control group ($p=0.001$ and $p=0.045$). When acute coronary syndrome groups compared to control; a positive correlation was found between chitotriosidase activity and hs-CRP ($r=0.21$, $p=0.046$), troponin T ($r=0.25$, $p=0.016$), creatine kinase-MB ($r=0.20$, $p=0.059$).**

***Conclusion*:The activity of chitotriosidase is increased in acute coronary syndrome patients. Chitotriosidase is higher in ST-segment elevation myocardial infaction group than non ST-segment elevation myocardial infarction and unstable angina pectoris group.**

J Atheroscler Thromb, 2013; 20:134-141.

Key words; Acute coronary syndrome, Chitotriosidase, Macrophage, hs-CRP

Introduction

Rupture of atherosclerotic plaque and additional thrombus cause acute coronary syndrome. Coronary arterial inflammation is commonly seen in acute coronary syndrome (ACS). According to studies, the prevalence of ruptured plaque occurs in parallel with the elevation of serum inflammatory markers. Measurement of inflammatory markers also enables risk assessment of the disease[1)]. The process that leads to arterial inflammation is involved in many different cell types. Neutrophils, white blood cells such as macrophages

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Received: July 6, 2012
Accepted for publication: July 26, 2012

and T cells, are key components of any inflammatory process, and may lead to the presence of various pro-inflammatory mediators. Chitotriosidase (CHIT), with a weight of 50 kDa, a human chitinase member of family 18 glycosylhydrolase, is one of the most abundant proteins secreted in plasma by activated macrophages, neutrophils[2-3]; however, it is not secreted from lymphocytes and monocytes. One third of these enzymes undergo proteolysis, forming 39 kDa fragments that are collected in lysosomes[4]. This activity has been proposed as a biochemical marker of macrophage accumulation and activity in several lysosomal lipid-storage diseases, including sphingolipidoses such as Nieman Pick, GM-gangliosidosis, and Krabbe disease[5-7]. Recently, some studies have demonstrated a significant association between chitotriosidase activity and atherosclerosis[8-10].

Studies related to CHIT, which is derived from active macrophages and plays a role in arterial inflammation, are very new. In a few studies, serum CHIT activity was investigated in patients with coronary artery disease and previously stable angina. Serum CHIT activity was found to be higher in those patients than in healthy people. No study has yet been performed on the increase in CHIT activity under different definitions of ACS, such as unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI), and the activity of CHIT in the classification of ACS. The purpose of this study was to evaluate differences in CHIT activities among ACS patients with a diagnosis of UAP, NSTEMI or STEMI. In addition, we investigated the relationship between serum CHIT activity and inflammatory markers such as cardiac enzymes and hs-CRP.

Methods

Study Design and Subjects

The study protocol was approved by the Ethics Committee of Ege University and written informed consent was given by all patients. The study was performed between 12th Jaunary and 15th June 2010. Thirty STEMI, 30 NSTEMI, 30 UAP consecutive patients and a control group ($n=30$) were included. All the patients' histories were taken and detailed physical examinations were performed on hospital admission. ECGs were taken on first admission to the coronary intensive care unit. All the patients were classified into STEMI, NSTEMI and UAP groups according to ST segment elevation, depression, T-wave changes (biphasic T, T-wave inversion) in first captured ECGs and cardiac enzyme elevation in the first 24 hours. Patients with fasting blood glucose 126 mg/dl and above, HbA1c >7 were considered diabetes mellitus (DM). Admission blood pressure, ECG rhythm, pulse rate, medications and risk factors were recorded. Body weights and heights of all patients in the study were measured and body mass index (BMI= weight/(height)^2) was calculated. Vascular lesions of the patients with acute coronary syndromes, who underwent CAG in the cardiac Catheterization Laboratory, were examined. In-hospital and 3-month mortalities were recorded. TIMI risk score was calculated. Patients with acute/chronic renal or hepatic insufficiency, systemic inflammatory disease, malignancy, acute infection, neurological disease leading to dementia, withdrawal of patients from the study, hepatitis, cerebrovascular event in any period of life, the presence of previously diagnosed lysosomal storage disease, pregnancy, lactation, pulmonary embolism, congestive heart failure, hypothyroidism, hyperthyroidism were also excluded.

Diagnosis of Acute Myocardial Infarction

ACS was diagnosed with ST-segment elevation in two or more adjacent leads (≥2 mm chest leads or ≥1 mm limb leads), ST-segment depression, T-wave changes in ECG; typical chest pain lasting more than 30 minutes and increase or decrease in myocardial enzymes.

Protocol for CAG

Selective CAG was performed by the Judkins technique through the femoral approach with 6F catheters. Stenosis severity was determined by visual estimation (in ≥2 orthogonal views) and angiographic findings were assessed by experienced cardiologists. Operators reading the angiograms were unaware of the results of any laboratory analyses. The number, location, and severity of lesions in each arterial segment were recorded.

Blood Sampling

Overall, plasma CHIT activity and hsCRP levels of 120 subjects were measured (81 men, 39 women) at first hospital admission. Blood samples were taken when the patients came to the Emergency Department with a diagnosis of acute coronary syndrome. Serial creatine kinase (CK), creatine kinase-MB (CK-MB) and troponin tests were performed in the first 24 hours. Complete blood count, renal, liver and thyroid function tests were evaluated in terms of the criteria for admission to the study. Blood samples were left to clot and the serum was separated by centrifugation within 2 h of sampling. All serum samples were stored

Table 1. Comparison of acute coronary syndrome group and control group according to individual factors

DIAGNOSIS	STEMI		NSTEMI		UAP		CONTROL GROUP		TOTAL		*P* VALUE
INDIVIDUAL FACTORS											
	M	F	M	F	M	F	M	F	M	F	
SEX*	27	3	19	11	21	9	14	16	81	39	0.04
	9%	10%	63.3%	36.7%	70%	30%	46.7%	53.3%	67.5%	32.5%	
AGE (year)	56.40 ± 10.77		63.80 ± 12.05		61.17 ± 10.83		46.07 ± 8.13		56.86 ± 12.43		NS□
WEIGHT (kg)	82.00 ± 15.54		77.90 ± 11.70		79.90 ± 11.44		70.30 ± 7.58		77.53 ± 12.56		0.04
LENGHT (cm)	169.87 ± 5.77		167.63 ± 8.09		170.27 ± 9.25		169.00 ± 6.09		169.19 ± 7.41		NS□
BMI** (weight/length^2)	28.42 ± 5.35		27.74 ± 4.20		27.85 ± 4.04		24.55 ± 2.07		27.14 ± 4.32		0.02
Systolic Blood Pressure (mmHg)	143.17 ± 42.11		144.17 ± 23.08		147.83 ± 20.79		119.33 ± 11.27		138.63 ± 28.74		0.001
Diastolic Blood Pressure (mmHg)	86.33 ± 23.52		87.17 ± 14.48		89.50 ± 11.39		74.67 ± 9.64		84.42 ± 16.54		< 0.002
Heart rate (minutes)	77.07 ± 18.96		79.17 ± 16.70		76.83 ± 20.57		76.73 ± 8.68		77.45 ± 16.67		0.93
LDL-C (mg/dL)	127.93 ± 38.63		108.10 ± 35.469		115.10 ± 47.115		116.70 ± 21.895		116.95 ± 35.77		NS□
HDL-C (mg/dL)	40.0 ± 6.81		41.20 ± 15.52		43.97 ± 9.64		53.83 ± 15.83		44.75 ± 11,95		0.001
TG (mg/dL)***	142.30 ± 64.82		160.80 ± 76.13		176.80 ± 125.14		103.03 ± 30.14		145.73 ± 74.05		0.001
T-C(mg/dL)****	195.87 ± 43.91		179.87 ± 45.21		191.83 ± 47.95		188.47 ± 28.39		189.01 ± 41.36		NS□

*SEX: M: Male, F: Female
**BMI: Body Mass Index
***TG: Triglyceride
****T-C: Total Cholesterol
□NS: Not significant

at −70℃ until analysis.

Biochemical Analysis

Quantification of Lipids

Total cholesterol (TC) and triglyceride (TG) levels were quantified enzymatically with a Beckman Synchron LX 20 analyzer (Boehringer Mannheim, Mannheim, Germany). High-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of apolipoprotein B-containing lipoproteins with Mg++ phosphotungstate (Boehringer Mannheim). Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula.

Chitotriosidase Enzyme Assay

Chitotriosidase activity was measured by incubating 5·l serum with 100·l of 22·mol/L 4-methylumbelliferyl-··-DN,N',N" triacetylchitotriose (MU-(··-GlcNAc)$_3$; Sigma Chemical Co, St Louis, MO, USA) as the substrate in Mellvain's phosphate-citrate buffer, pH 5.2 for 1h at 37℃ (modified from Hollak *et al.*[11]). The reaction was terminated by adding 120·l of 0.5 mol/L Na_2CO_3-$NaHCO_3$ buffer, pH 10.7, and the fluorescence of 4-methylumbelliferone was measured with a fluorimeter (Titertek; excitation 355 nm, emission 460 nm).

hsCRP Assay

Serum concentrations of hsCRP were measured by the Behring BN II Nephelometer (DADE Behring, Marburg, Germany) and expressed as milligrams per liter.

Statistical Analysis

The statistical analyses were performed using SPSS statistical program version 18.0 (SPSS, Chicago, IL, USA). The suitability of the normal distribution of all parameters was measured by the Shapiro-Wilk test. All values are expressed as the mean ± SD unless otherwise stated. T-test was used in the analysis of the difference of two groups and ANOVA was used in the normal distribution of data matching among the three groups for statistical comparison. Respectively, the Mann-Whitney *U* and Kruskal-Wallis tests were used for all variables that did not present with normal distribution. The "cut-off" value was calculated by analyzing the ROC.

The chi-square test was used in the comparison of percentage data and the paired *t* test was used to assess the temporal change of the dependent variables. Pearson's correlation or Spearman's correlation coefficient was calculated to investigate the relationship between the variables. A value of $p < 0.05$ was consid-

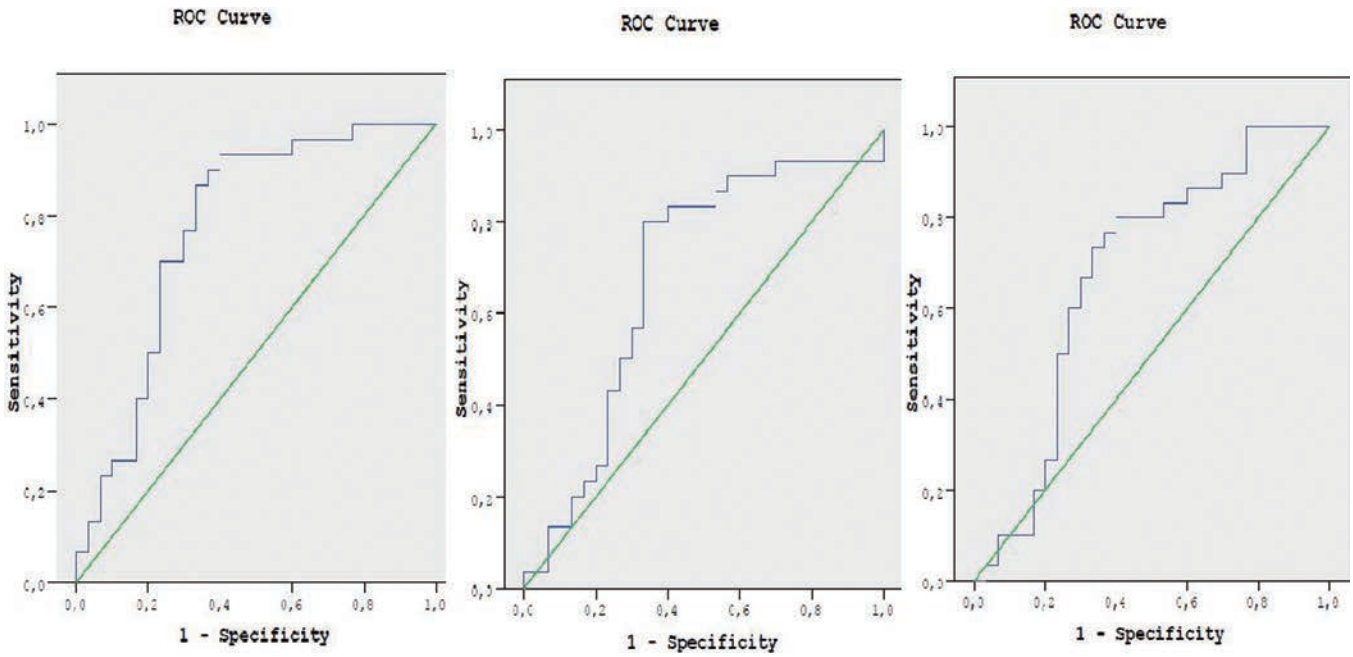

Fig. 1. ROC analysis of CHIT activity of STEMI, NSTEMI, UAP.

Left: ROC analysis of CHIT activity of STEMI, middle: ROC analysis of CHIT activity of NSTEMI, right: ROC analysis of CHIT activity of UAP.

ered significant for all analyses.

Results

The study population comprised 120 subjects (81 men, 39 women), who were classified into four groups: 30 STEMI patients, 30 NSTEMI patients, 30 UAP patients, and 30 patients in the control group. Statistically significant differences were found between the acute coronary syndrome patients and patients in the control group in relation to sex, weight, and BMI ($p=0.004$, $p=0.004$, $p=0.02$); however, there were no statistical differences among the STEMI, NSTEMI, and UAP groups. Basal systolic and diastolic blood pressure readings were stastistically higher in the ACS groups than in the control group ($p=0.001$, $p<0.002$). The HDL-C value was lower and TG value was higher in the ACS groups, and each finding was found to be statistically significant ($p=0.001$, $p=0.001$) (**Table 1**).

Serum Chitotriosidase Activity

ROC analysis was performed for each group. The areas under the curve (AUC) for STEMI, NSTEMI and UAP were 0.774 ($p>0.001$), 0.678 ($p=0.018$) and 0.678 ($p=0.018$), respectively (**Fig. 1**). The cut-off values for each group were 84.46, 80.85 and 82.12 mmol·ml-1·h-1 with 80% sensitivity and 67% specificity, respectively. As a result of the ROC analysis, the levels of CHIT in all ACS patients were calculated as 82.00 mmol·ml-1·h-1 as a cut-off value, with 83% sensitivity and 72% specificity. Serum CHIT activitity was present in each of the four studied groups. Statistically significant step increases in serum CHIT activity were observed in all ACS groups compared to the control group (88.85 ± 23.08 mmol·ml-1·h-1). Serum CHIT activity was 96.11 ± 19.77 mmol·ml-1·h-1, 85.52 ± 27.5 mmol·ml-1·h-1 and 84.92 ± 20.07 mmol·ml-1·h-1 for patients with STEMI, NSTEMI, and UAP, respectively; however, it was 68.47 ± 28.44 mmol·ml-1·h-1 in control-group subjects. There was a significant difference in serum CHIT activity between the subjects with ACS and the control group ($p<0.001$). Differences in serum CHIT activity were also statistically significant between the study groups based on STEMI-control and NSTEMI-control groups ($p=0.001$, $p=0.045$); however, no statistical differences were found between the UAP group and the control group ($p=0.06$). When ACS groups were compared with each other, there were no statistically significant differences (STEMI-NSTEMI $p=0.22$, STEMIUAP $p=0.18$, NSTEMI-UAP $p=1.0$) (**Table 2**).

Chitotriosidase and Demographic Characteristics

CHIT activity was detected to be 88.36 ± 24.79

Table 2. Comparasion of all groups according to biochemical factors

DIAGNOSIS BIOCHEMICAL MARKERS	STEMI	NSTEMI	UAP	CONTROL GROUP	*P* VALUE
Hs-CRP mg/dL	2.79 ± 1.98	3.34 ± 1.96	1.13 ± 1.79	0.15 ± 0.096	0.001
Chitotriosidase (mmol · ml-1 · h-1)	96.11 ± 19.77	85.52 ± 27.56	84.92 ± 20.07	68.47 ± 28.44	0.001
Troponin T (ng/mL)	5.443 ± 3.473	1.576 ± 1.568	0.011 ± 0.0053	0.01	0.001
CK-MB (U/L)□	159.0 ± 110.04	69.83 ± 63.38	16.43 ± 4.59	13.57 ± 3.99	0.001

□CK-MB: Creatine kinase MB

Table 3. Chitotriosidase and Demographic Characteristics

	Chitotriosidase mmol · ml-1 · h-1	*p* value
Sex		
Female (*n* = 23)	90.28 ± 17.58	0.21
Male (*n* = 67)	88.36 ± 24.79	
Hypertension (*n* = 56)	90.01 ± 20.00	0.57
Hyperlipidemia (*n* = 42)	88.41 ± 25.93	0.86
Type 2 Diabetes Mellitus (*n* = 30)	86.23 ± 24.32	0.44
Cigarette Smoking (*n* = 63)	89.76 ± 23.15	0.57
Family History (*n* = 59)	90.87 ± 18.52	0.25
CAD History* (*n* = 44)	87.89 ± 24.35	0.70
CABG History** (*n* = 17)	87.10 ± 20.17	0.73
Drinking Alcohol (*n* = 20)	74.08 ± 27.72	0.031

*CAD: Coronary Artery Disease
**CABG: Coronary Artery By-pass Graft

mmol · ml-1 · h-1 in men and 90.28 ± 17.58 mmol · ml-1 · h-1 in females. Higher CHIT activity in women was not statistically significant ($p = 0.21$). CHIT activity in patients with hyperlipidemia (88.41 ± 25.93 mmol · ml-1 · h-1), DM (86.23 ± 24.32 mmol · ml-1 · h-1), and alcohol drinking (74.08 + 27.72 mmol · ml-1 · h-1), was found to be lower, but it was only statistically significant in those who were drinking alcohol ($p = 0.86$, $p = 0.44$, $p = 0.031$). When logistic regression analysis was performed, systolic BP, smoking, and age were found to be factors that might affect the level of CHIT activity ($p = 0.011$, $p = 0.012$, $p = 0.033$) (**Table 3**).

Chitotriosidase and Medical Treatment

CHIT activity was found to be higher in patients who were taking aspirin, but it was not statistically significant (90.58 ± 22.07 mmol · ml-1 · h-1, $p = 0.44$).

Chitotriosidase and Biochemical Markers

An inversely proportional relationship was found between CHIT activity and the increase of HDL-C ($p = 0.020$). There was no relationship between CHIT activity and HbA1c or fasting blood glucose ($p = 0.05$, $p = 0.049$). In addition, there was no statistical difference between the CHIT activity level and LDL-C, TG or Tc ($p = 0.90$, $p = 0.054$, $p = 0.22$). A significant positive correlation was found between CHIT activity and hs-CRP ($r = 0.21$, $p = 0.046$), troponin T ($r = 0.25$, $p = 0.016$), and CK-MB ($r = 0.20$, $p = 0.059$) when all ACS groups were compared.

Chitotriosidase and ECG

There was a correlation between CHIT activity and the derivation number of ST segment elevation on ECG in the STEMI group ($p = 0.039$). According to the type of MI, CHIT activity was found to be higher in the anterior MI group than in the non-anterior MI group (105.13 ± 20.04 mmol · ml-1 · h-1); however, it was not statistically significant ($p = 0.063$).

Chitotriosidase and Coronary Artery Disease

There was no statistically significant difference between the number of diseased coronary arteries and

Table 4. Number of diseased coronary arteries in acute coronary syndrome groups

DIAGNOSIS NUMBER OF DISEASED CORONARY ARTERIES	STEMI CHIT Level mmol · ml-1 · h-1	NSTEMI CHIT Level mmol · ml-1 · h-1	UAP CHIT Level mmol · ml-1 · h-1	*p* value
1 Vessel	104.17 ± 14.57 *n* = 11	91.65 ± 8.78 *n* = 10	76.04 ± 23.92 *n* = 5	0.076
2 Vessel	84.93 ± 10.38 *n* = 5	84.10 ± 62.00 *n* = 6	87.74 ± 27.90 *n* = 8	0.95
3 Vessel	99.07 ± 8.33 *n* = 7	80.45 ± 33.76 *n* = 6	96.02 ± 10.57 *n* = 7	0.51

CHIT activity ($p = 0.57$) (**Table 4**).

Chitotriosidase and TIMI Risk Score

A positive correlation was found between CHIT activity and the TIMI risk score ($r = 0.21$, $p = 0.040$).

Chitotriosidase and Cardiovascular Events

In this study, no statistically significant difference was found between CHIT activity and the development of arrhythmias during hospitalization ($p = 0.054$) and cardiovascular complications after MI ($p = 0.67$), with three-month mortality. As all the cardiovascular events were evaluated together, no relationship was found between CHIT activity and the events ($p = 0.58$).

Discussion

Laboratory and prospective clinical studies[12-14] have recently reinforced the inflammatory theory proposed by Ross *et al.*[15] which states that each step in molecular and cellular responses leading to atherosclerosis is an inflammatory process in which activated macrophages seem to play a central role. Macrophages are present in all phases of atherogenesis and have been shown to be markers of atherosclerotic plaque formation[16]. Many cytokines and inflammatory mediators are formed in the breakdown of atheroma plaque. Among the markers of inflammation, hs-CRP is the most extensively studied and it is well-documented by several studies that high levels of hs-CRP are associated with an elevated risk of coronary, cerebral and peripheral vascular diseases[17-19]; however, there are few studies about CHIT and atherosclerosis[20]. To our knowledge, this is the first clinical study about CHIT association with ACS. In this study, we analyzed two markers of activated macrophages in ACS, CHIT and hs-CRP, and their relationship between troponin T and CK-MB.

CHIT is synthesized exclusively by activated macrophages, and its enzymatic activity is elevated in the serum of patients with diseases in which macrophages are activated by the accumulation of glycosphingolipid, iron, and glycogen. A small number of studies have also demonstrated an association between macrophage CHIT expression and atherosclerosis, suggesting a possible role as an atherosclerotic marker[8-10]. Boot *et al.* (1999) documented that CHIT activity is increased up to 55-fold in extracts of atherosclerotic tissue, demonstrating a clear association between CHIT expression and lipid-laden macrophages in the atherosclerotic human vessel wall[9]. Plasma CHIT was also found to be associated with the extent of plaque in mice fed a high-fat, atherogenic diet[10]. Artieda *et al.* investigated the association of serum CHIT activity with atherosclerosis in 153 patients with atherothrombotic stroke and in 124 patients with UAP. Serum CHIT activity was more prominent in stroke patients than in patients with ischemic heart disease, suggesting more widespread atherosclerosis. In a related study, Artieda *et al.* (2007) also showed that CHIT activity predicts the risk of new adverse cardiovascular events within a follow-up period of four years[21]. Canudas *et al.* (2001) reported that serum CHIT activity is not associated with lipid levels before and after treatment with statins, which suggests that plasma lipid level alteration does not affect the macrophage CHIT expression level *in vivo* and is in accordance with our study, showing no correlation between blood lipid levels and CHIT activity[22]. In our study, hs-CRP and CHIT activity were analyzed in acute coronary syndrome and compared with CK-MB and troponin levels. CHIT activity was found to be significantly higher in acute coronary syndrome groups than in the control group. CHIT activity was listed as STEMI > NSTEMI > UAP. CHIT activity showed a

significant correlation with CK-MB and troponin levels in acute coronary syndrome patients. In addition, we found a cut-off value (82 mmol·ml-1·h-1) with 83% sensitivity and 72% specificity in ACS patients in this study. The increased activity of CHIT, a product of activated macrophages, could be affected by the inflammatory process of the plaque and the exposure of the plaque contents after its rupture. Because cytokines and inflammatory mediators are formed in the breakdown of atheroma plaque, further studies should be performed to elucidate plaque rupture and CHIT activity.

As in our findings, Artieda and Kurt *et al.* (2003; 2007) found a correlation between age and serum CHIT activity[8, 23]; however, Karadag *et al.* (2008) found no correlation between age and serum CHIT activity[20]. Despite using a similar method of measurement, the serum CHIT activity was relatively low in the study population of Artieda *et al.* (2003) in comparison with the present patient population. This difference can be explained by differences in CHIT activity observed between different ethnic populations, which may be attributable to distinct genotype distributions. CHIT activity was higher in women than in men. This result may be associated with estrogen and progesterone in women. Also, CHIT activity was found to be lower in patients who drank alcohol. We explain this result as follows: drinking alcohol limits macrophage activation[24]. In addition to these findings, CHIT activity was found to be higher in patients taking acetyl salicylic acid. We suggest that increased CHIT activity may be a reflection of the activation of macrophages with acetyl salicylic acid.

When CHIT activity of ACS patients was compared in terms of the extent of vascular disease after coronary angiography, no relationship was detected. On the other hand, Karadag *et al.* (2008) found an association of serum CHIT activity with atherosclerosis in humans with the extent of CAD with stable CAD according to coronary angiography[20]. In our study, we demonstrated the association of increased serum CHIT activity with elevated troponin, CK-MB, and hs-CRP in ACS patients; however, increased CHIT activity did not show any superiority in predicting cardiovascular events and post-ACS complications.

Conclusion

In this study, a cut-off (82 mmol·ml-1·h-1) value with 83% sensitivity and 72% specificity was found for CHIT activity in ACS patients for the first time. CHIT activity >82 mmol·ml-1·h-1 was significant in the diagnosis of ACS, and it was as high as hs-CRP, CK-MB, and troponin levels, but it seemed to have no superiority in predicting short-term cardiovascular events according to other traditional indicators. Our findings support previous suggestions that inflammation is a crucial factor in atherogenesis and ACS. High CHIT activity in ACS may reflect the release of the content of ruptured plaque. We believe that the relationship between serum CHIT activity and atherosclerosis represents a new opportunity for using serum CHIT activity as a marker for ACS. Although our findings require further confirmation through future studies, serum CHIT activity shows remarkable potential as a quantitative indicator of the extent of disease, besides being a marker of the presence of disease.

Study Limitations

The peak level of CHIT activity and peak level time were not analyzed.

Funding

Funding for this work was obtained from the Department of Cardiology and Biochemistry.

Conflict of Interest

None.

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