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Relation of heart-type fatty acid-binding protein with the extent and severity of atherosclerosis in patients with non-ST elevation acute coronary syndrome

ST segment yükselmesiz akut koroner sendromlu hastalarda kalp tipi yağ asidi bağlayıcı proteinin koroner arter hastalığının yaygınlık ve ciddiyeti ile ilişkisi

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ABSTRACT

Objectives: The relationship between markers of myocardial ischemia and severity of coronary artery disease (CAD) has been investigated in several studies. In this study, we examined the relationship between severity of CAD and heart-type fatty acid-binding protein (H-FABP), a new marker of ischemia in patients with non-ST-segment elevation acute coronary syndrome (ACS).

Study design: This prospective study comprised 49 patients who were referred to the emergency room with a diagnosis of non-ST elevation myocardial infarction. Troponins, creatine kinase-MB, lactate dehydrogenase, and aspartate aminotransferase levels were measured quantitatively, while blood H-FABP levels were measured qualitatively within the 4th-8th hour from the onset of symptoms. All patients underwent coronary angiography within 72 hours after admission. Clinical and coronary angiographic characteristics of H-FABP positive and negative patients were compared. Gensini and SYNTAX scores were used to determine the severity of CAD.

ÖZET

Amaç: Miyokart iskemisi belirteçleri ile koroner arter hastalığı ciddiyetinin ilişkisi birçok çalışmada araştırılmıştır. Bu çalışmada, ST segment yükselmesiz akut koroner sendromlu (AKS) hastalarda yeni bir iskemi belirteci olan kalp tipi yağ asidi bağlayıcı protein (KYABP) ile koroner arter hastalığı (KAH) ciddiyetinin ilişkisi incelendi.

Çalışma planı: Çalışma ileriye dönük ve kesitsel olarak tasarlandı. Çalışmaya acil servise başvuran ST segment yükselmesiz AKS tanısı konan 49 hasta alındı. Semptom başlangıcının 4.-8. saat aralığında alınan kan örneğinden KYABP kalitatif olarak; troponin, kreatin kinaz-MB, laktat dehidrogenaz ve aspartat aminotransferaz düzeyleri kantitatif olarak ölçüldü. Tüm hastalara başvurudan sonraki ilk 72 saat içinde koroner anjiyografi yapıldı. KYABP pozitif ve negatif hastaların demografik özellikleri ve biyokimyasal değerleri, TİMİ risk skoru ve koroner anjiyografi özellikleri karşılaştırıldı. KAH ciddiyeti Gensini ve SYNTAX skorlaması ile değerlendirildi.

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Results: There were no statistically significant differences in mean age, gender distribution, risk factors for CAD, ischemic changes on ECG, or Gensini and SYNTAX scores between the H-FABP-negative and -positive groups ($p>0.05$). The duration of chest pain in the H-FABP-positive group was significantly longer than in the negative group ($p<0.001$). Troponin, CK-MB, and AST levels as well as thrombolysis in myocardial infarction (TIMI) risk scores were found to be significantly higher in the H-FABP-positive group ($p<0.05$). Conclusion: H-FABP is a useful marker for the diagnosis and risk evaluation of patients with non-ST elevation ACS. However, it is insufficient in evaluating the severity of CAD.

Bulgular: KYABP negatif grup ile pozitif grup arasında yaş ortalamaları, cinsiyet dağılımı, eşlik eden KAH risk faktörleri ve iskemik EKG değişikliği yönünden istatistiksel anlamlı farklılık görülmedi ($p>0,05$). Göğüs ağrısı süresi KYABP pozitif olan grupta negatif gruptakinden anlamlı olarak daha yüksek bulundu ($p<0.001$). KYABP negatif ve pozitif grup arasında lipit profili, açlık kan şekeri, Gensini skoru, SYNTAX skoru, total lezyon ve trombüs varlığı yönünden istatistiksel anlamlı fark görülmedi ($p>0,05$). TİMİ risk skoru KYABP pozitif grupta anlamlı olarak yüksek bulundu ($p<0,05$).
Sonuç: Bulgularımız KYABP'nin, ST segment yükselmesiz AKS'li hastaların tanısı ve risk değerlendirilmesinde kullanılabileceği görüşünü desteklerken, KAH'nın ciddiyetini değerlendirmede yetersiz kaldığını düşündürmektedir.

Abbreviations:

ACS *Acute coronary syndrome*
AMI *Acute myocardial infarction*
CAD *Coronary artery disease*
CPR *Cardiopulmonary resuscitation*
H-FABP *Heart-type fatty acid-binding protein*
MCE *Major cardiac event*

Biochemical markers known to be released from cadaveric heart muscle cells have begun to play important roles in the establishment of the diagnosis of acute coronary syndrome (ACS). [1,2] Since troponin is highly sensitive in the detection of even very small areas of destructive changes, and also rises specifically almost always in cases with myocardial ischemia, in addition to its use in the risk evaluation of ACS, it is preferred as a biochemical marker in the diagnosis of ACS.[3,4] Recent investigations have been performed with some biochemical markers which might be alternatives to troponin. Particularly, within the the last 20 years, the roles of newly-developed biochemical markers in the establishment of diagnosis, and treatment modality have been analyzed. These novel markers conceivably might ensure better characterization of ACS pathophysiology which indirectly leads to the development of specific treatment modalities. Besides, use of these markers in combination with troponin might provide more complementary information about diagnosis, and risk evaluation.

Firstly, in the year 1988, researchers revealed release of heart-type fatty acid-binding protein (H-FABP) which is a low-molecular weight, cytosolic, soluble non-enzymatic secretion from ischemic myocardial tissue in patients with acute myocardial infarction (AMI) .[5,6] During the early stage of the disease, it is released from the myocardial tissue in response to myocardial ischemia, and consequently its plasma concentration rises. Within one and a half hour after the onset of symptoms of myocardial infarction (MI) its plasma levels begin to increase, peaks at 6-8 hours, and it is completely eliminated from the body at 24-36 hours.[7] Thanks to its practical applicability at bedside, and rapid retrieval

of analytical results, it is possible to establish a diagnosis, and determine risk factors in a short time. Its levels increase in the early stage of the disease secondary to myocardial ischemia, and it is more specific to myoglobin which all constitute other advantages of H-FABP tests.

Although coronary angiography is an inadequate technique in the visualization of vulnerable plaques predisposing to ACS, it is still the most important, and prevalent diagnostic tool used for the demonstration of extent, and severity of coronary artery disease (CAD). Angiographically specified location, size, complexity, extent of the lesion, degree of related stenosis, and presence of a thrombus (thrombi) are important parametres indicating severity of CAD. Besides, many risk factors have been developed to be used in the evaluation of angiographic severity of CAD.

Assessment of severity of coronary artery disease can canalize evaluation of the risk in the early stage of the disease in non-ST-segment elevation ACS, and its treatment. Therefore, a biochemical marker associated with extent, and severity of the lesions detected on coronary angiograms has a crucial importance. In this study in patients with non-ST- segment elevation ACS, the correlation between H-FABP, severity, and extent of CAD has been investigated.

PATIENTS AND METHOD

Selection of patients

The study had a prospective, cross-sectional design. A total of 50 patients diagnosed as non-ST-segment elevation ACS admitted into emergency service of the hospital were included in the study. One patient who didn't undergo coronary angiographic examination was excluded from the study. Approval for the study was obtained from the ethics committee of our hospital.

Diagnosis of non-ST- segment elevation ACS were based on the following criteria: 1) typical chest pain lasting more than 20 minutes, 2) newly-onset severe chest pain (at least Class III, according to the functional classification proposed by Canadian Cardiovascular Society, 3) conversion of previously stable angina pectoris into unstable angina pectoris 4) increase in the levels of biochemical markers of myocardial ischemia (troponin, CK-MB) , and 5) ischemic changes traced on electrocardiograms (ST-segment depression of > 0.5 mm in two or more than two adjacent derivations, and ischemic T negativity).

Exclusion criteria

The patients with the following criteria were excluded from the study: advanced age (>85 yrs), history of associated comorbidities (active infection, malignity, chronic diseases involving musculoskeletal system), refusal of an invasive intervention, contraindication for coronary angiography, chronic renal failure, higher (> 1.5 mg/dL) serum creatinine values, history of cerebrovascular event, trauma or surgery, cardiopulmonary resuscitation (CPR), MI, fibrinolytic treatment, and percutaneous coronary intervention.

Patients on antihypertensive therapy or those with systolic, and diastolic blood pressures of 140 mm Hg and 90 mm Hg respectively, on three different occassions were considered as hypertensive, and cases with LDL-C levels above 130 mg/dL were included in the

hyperlipidemic category. Individuals who habitually used cigarettes within the previous three years were considered as smokers.

Biochemical analysis

Blood samples drawn from eligible patients within 4-8 hours after the onset of symptoms were analyzed as for troponin, H-FABP, CKMB, LDH, and AST levels. Troponin, CKMB, LDH, and AST values were determined quantitatively, while H-FABP levels were measured semi-quantitatively using CardioDetect ® device (Convateca, Guerbet, Mika Medical Co, South Korea). Troponin (>0.06 ng/ml) and H-FABP (>7 ng/ml) levels above indicated values were considered as respective test positivities**.**

Calculation of TIMI risk score

TIMI risk scoring is based on seven measurable variables. These variables consisted of advanced age (≥ 65 yrs), ≥ 3 risk factors for CAD, angiographically detected ≥ 50 % stenosis, ST -segment alterations on admission (≥ 0.5 mm ST –segment depression) , ≥ 2 attacks of angina pectoris within the previous 24 hours, aspirin use, and higher levels of cardiac damage marker (troponin positivity) within the last 7 days. For each variable one point is assigned. Based on TIMI risk scores, the patients were evaluated as cases with high (≥ 5 pts) , moderate (3-4 pts), and low risk (0-2 pts).

Coronary angiography

Selective coronary angiography was performed using Judkins catheters inserted percutaneously through femoral rout under the guidance of Siemens® angiography device (Siemens, Munich, Germany). Left anterior descending artery (LAD), and circumflex artery (Cx) were visualized, and evaluated in at least 4, and 2 projections, respectively. Coronary reference segment was selected from proximal or distal to the lesion. Diameter of the coronary artery, and its luminal narrowing were measured, and calibrated in comparison with the diameter of the guiding catheter. Coronary stenosis was evaluated by two cardiologist blinded to the clinical manifestations of the patient.

Calculation of Gensini and SYNTAX scores

In the calculation of Gensini scores, the severity of angiographic stenosis was expressed in points assigned to different degrees of luminal narrowings as indicated in parenthesis (1 point, 0-25 %; 2 pts, 25-50 %; 4 pts, 50-75 %; 8 pts, 75-90 %; 16 pts, 90-99 %, and 32 pts for 100 % lesion [complete occlusion]) Subsequently, these assigned points were multiplied by coefficients determined for each main coronary artery, and each arterial segment, and the results were summed up. Scores of ≥ 20 points were evaluated as indicative of serious coronary artery disease.

For the calculation of SYNTAX scores, a program specially developed for this scoring system was used. According to this scoring system, arterial stenosis of ≥ 50 % were considered to be significant, while luminal narrowings less than 50 % were not included in calculations. Degree of coronary stenosis was considered in 2 groups as 50-99 % narrowing, and complete (100 %) occlusion. SYNTAX scores were rated as indicative of mild (0-22 pts), moderate (23-32 pts), and severe (≥ 33 pts) degrees of stenosis.

Table 1. Comparison of demographic characteristics, and biochemical values of H-FABP positive, and negative patients

Variable	Group1 H-ABP (–) (n=29)			Group 2 H-FABP (+) (n=20)			p
	n	%	Mean .±SD	n	%	Mean.±SD	
Age (yrs)			56.65±10.28			59.70±12.41	0.328
Gender (female)	4	13.8		4	20		0.563
Coronary artery disease (%)	6	20.7		7	35.0		0.265
Hypertension (%)	16	55.2		0	50		0.721
Diabetes mellitus (%)	7	24.1		9	45		0.126
Smoking (%)	9	31		9	45		0.319
Family history (%)	9	31		7	35		0.771
Hyperlipidemia (%)	11	37.9		8	40		0.884
Aspirin use (%)	6	20.7		8	40		0.141
EKG changes (%)	15	51.7		11	55		0.821
Total cholesterol (mg/dl)			187.17±49.56			185.10±55.91	0.535
LDL (mg/dl)			110.06±40.61			117.70±35.47	0.095
HDL (mg/dl)			39.34±6.98			40.25±8.27	0.862
Triglyceride(mg/dl)			167.48±79.17			146.40±53.46	0.404
Glucose (mg/dl)			107.53±36.52			118.20±53.41	0.272
Duration of pain (hrs)			0.76±1.00			3.06±2.04	**<0.001**
H-FABP sampling time (hrs)			6.85±1.69			7.31±0.88	0.265

H-FABP: Heart-type fatty acid binding protein; SD: Standard deviation ; CAD: Coronary artery disease ; LDL: Low-density lipoprotein ; HDL: High-density lipoprotein.

Table 2. Coronary artery severity scores, and levels of clinical risk in H-FABP positive, and negative patients

Variable	Group 1 H-FABP (–) (n=29)			Group 2 H-FABP (+) (n=20)			p
	n	%	Mean ± SD	n	%	Mean ± SD	
Gensini score			43.48±29.24			51.20±38.55	0.508
Gensini score>20	23	79.3		16	80.0		1.000
SYNTAX score			12.96±8.37			16.12±12.42	0.521
SYNTAX							0.684
Mild	24	82.8		16	80.0		
Moderate	4	13.8		1	5.0		
Severe	1	3.4		3	15.0		
TİMİ risk score			3.34±1.07			4.45±1.27	**0.002**

H-FABP, heart-type fatty acid binding protein; SD: Standard deviation

Statistical analysis

Normality of continuous variables was determined with Shapiro-Wilk test. Continuous variables were indicated as mean ± SD or medians. Descriptive values related to categorical data were expressed as numbers, and percentages. Regarding numerical characteristics demonstrating normal distribution, differences between H-FABP positive, and negative groups were compared using Student *t* test, and for those without normal distribution intergroup differences were analyzed with Mann-Whitney U-test. Besides, relationship between H-FABP groups, and categorical characteristics was analyzed using *chi*-square or Fisher's exact test as deemed to be appropriate. Margin of error in statistical analysis was 5 percent.

Analysis of data was performed using "SPSS for Windows" version 11.5 (SPSS Inc., Chicago, IL, US)

RESULTS

Eight (16.3 %) female, and 41 (83.7 %) male patients, in other words a total of 49 patients with a mean age of 57.89 ± 11.17 years were enrolled in the study. Mean duration of chest pain of the patients were 1.70±1.88 hours. H-FABP was measured after an average of 7.04±1.42 hours from the onset of symptoms. Demographic characteristics, and clinical findings of the patients with H-FABP positivity or negativity are given in Table 1. As seen in Table 1, demographic features, and biochemical values of the patients with H-FABP positivity or negativity were comparatively similar. In the group with H-FABP positivity, average duration of painful episodes was significantly longer ($p<0.001$).

CAD severity scores, and degrees of clinical risks in H-FABP positive, and negative patients are given in Table 2. In the H-FABP positive group, mean TIMI score was found to be significantly higher ($p=0.002$) (Figure 1).

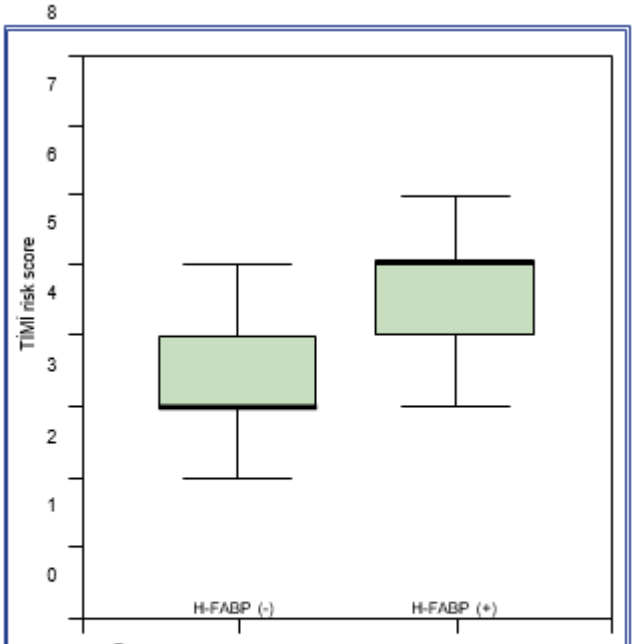

Figure 1. Comparison of patients with or without heart-type fatty acid binding protein (H-FABP) using TIMI risk scores Horizontal lines in the middle of each box represent median, upper , and lower lines indicate 25., and 75.percentiles, respectively.. T shaped shaped extensions over, and below the box represent minimal, and maximal TIMI risk scores.

Any statistically significant difference was not seen between groups with H-FABP (–), and H-FABP (+) regarding median Gensini score, frequency of elevated Gensini scores (> 20 pts), SYNTAX score, high, moderate, and low risk categories based on SYNTAX scores ($p>0.05$, Table 2). Besides, any significant correlation was

not seen between H-FABP positivity, and the number of affected vessels, complete occlusion or the presence of thrombus ($p>0.05$).

DISCUSSION

In the present study, in patients presented with non-ST- segment elevation ACS, a significant correlation was not observed between H-FABP values , and Gensini, and SYNTAX scores which display extent, and severity of CAD., while in the H-FABP positive group, TIMI risk scores were found to be relatively higher.

H-FABP was firstly proposed by Glatz et al.[5] in 1988 as a novel biochemical marker in the early diagnosis of AMI, and several studies have also demonstrated its diagnostic role in AMI. In these studies, diagnostic sensitivity (up to 80 %) of increased H-FABP levels within 30-210 minutes after the onset of symptoms has been displayed. However, diagnostic sensitivity of markers including. CK, CK-MB, and troponin within 6 hours was found to be 64 percent. Up to now, use of H-FABP in the early diagnosis, and risk evaluation of the patients with ACS has been investigated in many studies. Ishii et al.[8] conducted a study on 328 patients with ACS (241 AMI, and 87 non-ST- segment elevation ACS patients), and compared troponin, and H-FABP values regarding newly-onset cardiac events developed within a period of 6 months. H-FABP has been demonstrated as an independent risk factor for cardiac events which might occur within 6 months after the onset of symptomatic ACS, and also its superior prognostic value over troponin in the early hours following ACS episodes has been revealed.

In non-ST- segment elevation ACS, early diagnosis, and risk evaluation are important with respect to the determination of prognosis, and appropriate treatment. Symptoms of the patient, clinical, biochemical, and angiographic findings play important roles in the diagnostic process, and risk evaluation. Therefore, many clinical risk scores have been developed.[9-12] Accordingly, guidelines which have been renewed in consideration of the outcomes of the recent studies have promoted wider use of GRACE risk scores [13,14], however TIMI risk score is a prototype of clinical risk scores.[11] Its effectiveness has been proven in many studies, and its relatively easier applicability offers important advantages. In our study, H-FABP levels were higher in patients with elevated TIMI risk scores. This correlation indicates potential impact of H-PABP in the evaluation of risk in the early stage of non-ST- segment elevation ACS.

Coronary angiography is performed to determine extent of CAD, detect the culprit lesion responsible for ischemia, and ascertain the treatment modality. Although this technique falls short of demonstrating vulnerable plaques triggering symptoms of ACS, it is an important diagnostic tool in the evaluation of extent, and severity of CAD. To that end, many angiographic scoring systems have been developed. Among them Gensini scoring system named after its founder [15] is the most prevalent assessment tool for stenosis. In a study performed on angiographic scoring systems used in patients with ACS, effectiveness of Gensini, Leaman ve ACC/AHA scoring systems in the prediction of major unwanted cardiovascular events were analyzed. In this study Gensini score was found to be

correlated with major cardiac events (MCEs) both in the short, and long-term. Leaman score was associated with MCEs in the short term, while an association between mortality rates, and all of these three scoring systems was detected.[16] SYNTAX rating scale which displays number of lesions, their functional effects, and complexity of the lesion was originally defined in 2005, and developed especially for the SYNTAX study [17] According to this scoring system, higher scores indicate more complex lesions, necessity of sophisticated revascularization interventions, and a poor prognosis. Recent studies have demonstrated that higher SYNTAX scores (≥ 34 pts) are associated with cardiac mortality independent of age, gender, ACS, ejection fraction (EF), EURO score, and degree of revascularization.[18]

In our study where we have used relatively updated SYNTAX score in addition to classical Gensini scoring system, a significant correlation could not be found among H-FABP, Gensini, and SYNTAX scores. Still, a significant relationship could not be observed between other markers of ischemia, and these scores. This result is not altogether surprising. Although, number of angiographically critical stenosis are known to predict unwanted events ,[19] dimensions of coronary plaques, and severity of stenosis do not provide information about vulnerability of the plaques. Gensini scores increase in parallel with the severity of the lesion. In the majority of ACSs, stenotic severity of the responsible lesions is much lower. Falk et al.[20] demonstrated that most of the ACSs stemmed from lesions leading to < 50 % luminal narrowing, and indicated that in only 16 % of the patients, responsible lesion led to more than 70 % coronary stenosis.

Studies have demonstrated that nearly three-fourths of the infarction-related thrombi had developed from mildly or moderately stenotic plaques because of tendency of these thrombi to partially outward remodelling, and their higher prevalence relative to stenotic plaques.[20] Therefore, in most of cases with MI, acute attacks of myocardial infarction stem from hemodynamically insignificant, and probably asymptomatic preexisting atherosclerotic lesions. Data derived from clinical TIMI-IIIB[21], and FRISC-II[22] studies demonstrated the presence of single or multiple-stenotic (> 50 % luminal narrowing) vessel disease in 30-38, and 44-59 % of ACS patients, respectively. Coronary stenosis of more than 60 % was not seen in 19 % of the patients. Diffuse atherosclerotic infliltration was detected in 14-19 % of the cases without any concomitant significant coronary stenosis.[23]

In a similar study performed by Antman et al.[24] troponin I values, and angiographic results of the patients were compared, and the authors reported that troponin levels might be correlated with future coronary events rather than the number of affected vessels, and degree of luminal narrowing. Our findings are also in line with the results of these studies. Serious coronary stenosis, and complex lesions might not be invariable seen in non-ST- segment elevation ACS with increased levels of H-FABP, and other markers of ischemia.

Any difference was not observed among our findings with respect to the correlation between the number of affected vessels, complete occlusion, presence of thrombi, and H-FABP positivity. Lack of

any correlation between complete occlusion, and the presence of thrombus (thrombi) suggests that levels of H-FABP increase in mild ischemic conditions. However in addition to the usability of H-FABP as a diagnostic tool in the early stage of ACS patients with non-ST segment elevation, more comprehensive studies should be performed on this issue.

Main limitations of our study are scarcity of patient population, lack of specificity of H-FABP only for cardiac entities, and its narrow diagnostic range. It can be hardly useful in cases with skeletal muscle damage during the course of acute ischemia, and in medical procedures including intramuscular injections, electrical cardioversion, and traumatic CPR. Still, potentially higher levels of H-FABF have been demonstrated in healthy individuals after forceful exercises. Besides, its levels may rise in cardiac, and non-cardiac surgical interventions. Since it is eliminated through renal route, false-positive results can be obtained in renal insufficiency. Besides, non-visualization of large plaques embedded in the arterial wall on angiograms constitutes limitations of the Gensini, and SYNTAX grading systems. In such cases, intravascular ultrasound which might be not always on hand, can be useful.

In conclusion, findings of this study support the viewpoint that suggests the applicability of H-FABP in the establishment of early diagnosis, and risk evaluation in ACS patients with non-ST-segment elevation. On the contrary, it is conceivably inadequate in the assessment of the extent, and severity of CAD.

Conflict of Interest: None declared

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Key words: Acute coronary syndrome; coronary artery disease; coronary angiography; heart-type fatty acid-binding protein; myocardial ischemia.

Anahtar sözcükler: Akut koroner sendrom; koroner arter hastalığı; koroner anjiyografi; kalp tipi yağ asidi bağlayıcı protein; miyokart iskemisi.