Heart-type fatty acid binding protein level in familial Mediterranean fever

Ailevi Akdeniz ateşinde kalp tipi yağ asidi bağlayıcı protein düzeyleri

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ABSTRACT

Objectives: Familial Mediterranean fever (FMF) is an autosomal recessive disorder and the most frequent periodic syndrome characterized by recurrent attacks of polyserositis. Heart-type fatty acid-binding protein (h-FABP) is an intracellular molecule engaged in the transport of fatty acids through the myocardial cytoplasm and a rapid marker of myocardial injury. FMF is an autoinflammatory disease characterized by ongoing inflammatory activity. Inflammation also plays an important role in the development and progression of atherosclerosis in some rheumatic diseases. We aimed to investigate markers of atherosclerosis in patients with FMF by the measurement of serum h-FABP and malondialdehyde levels (MDA).

Study design: Forty consecutive patients with FMF and twenty healthy volunteers were selected to participate in the study. The diagnosis of FMF was based on Tel-Hashomer criteria. Serum h-FABP and MDA levels were determined to examine the association.

Results: The mean h-FABP level in FMF patients was significantly higher than the normal population (4.89±0.83 *vs.* 3.06±2.13 ng/ml, p<0.01). The mean platelet volume was significantly higher in FMF patients than in the normal group (8.87±0.99 *vs.* 8.22±0.45 fl, p=0.04). Serum MDA levels were the same between the groups (1.08±0.66 *vs.* 1.08 ± 0.33 nmol/ml, p=0.99). h-FABP and MDA levels were the same in FMF patients with an acute attack and during an attack free period.

Conclusion: Our results show that h-FABP increases in patients with FMF. Higher h-FABP levels may lead to increased atherosclerotic propensity in FMF, independent of the oxidative stress status of these patients.

ÖZET

Amaç: Ailevi Akdeniz ateşi (AAA) tekrarlayan poliserozite bağlı ataklarla kendini gösteren otozomal çekinik bir hastalık olup en sık görülen dönemsel sendromdur. Kalp tipi yağ asidi bağlayıcı protein (KYABP) kalp kası hücresi sitoplazmasındaki yağ asitlerinin taşınmasında görevli hücre içi bir molekül olup kalp kası hasarının hızlı bir belirtecidir. AAA devamlı yangısal aktivite ile seyreden özyangısal bir hastalık olduğundan ve bazı romatizmal hastalıklarda yangı damar sertliği gelişimi ve ilerlemesinde önemli rol oynadığından, AAA hastalarında serum KYABP ve malondialdehit (MDA) düzeylerini ölçerek damar sertliğinin belirteçlerini araştırmayı amaçladık.

Çalışma planı: Ailevi Akdeniz ateşli kırk hasta ve yirmi sağlıklı gönüllü çalışma topluluğunu oluşturmak için seçildi. AAA tanısı Tel-Hashomer belirteçlerine göre konuldu. İlişkiyi araştırmak için serum KYABP ve MDA düzeyleri ölçüldü.

Bulgular: Ailevi Akdeniz ateşli hastalarda ortalama KYABP düzeyleri normal bireylere göre anlamlı olarak daha yüksekti (4.89±0.83 ve 3.06±2.13 ng/ml, p<0.01). AAA'lı hastalarda ortalama trombosit hacmi de normal bireylere göre anlamlı olarak daha yüksek bulundu (8.87±0.99 ve 8.22±0.45 fl, p=0.04). Gruplar arasında serum MDA düzeyleri farksızdı (1.08±0.66 ve 1.08±0.33 nmol/ml, p=0.99). AAA'lı hastalarda akut atak sırasında ve ataksız dönemlerde KYABP ve MDA düzeyleri yönünden de fark bulunmadı.

Sonuç: Ailevi Akdeniz ateşli hastalarda saptanan KYABP düzeyindeki artış bu hastalardaki oksidatif stres durumundan bağımsız olarak, AAA'de artmış damar sertliği yatkınlığına işaret ediyor olabilir.

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Familial Mediterranean fever (FMF) is an autosomal recessive disease manifested by recurrent attacks of serositis (peritonitis, pleuritis, pericarditis, synovitis/arthritis), fever and characterized by clinical, histological and laboratory evidence of inflammation.

Although FMF presents with exacerbations and attack free periods, it has been demonstrated that there is sustained inflammation during attack-free periods in FMF patients.[1,2] There have been many studies demonstrating cardiovascular involvement in patients with FMF. Most familiar of these is pericarditis at a ratio of 1.4%. It has been demonstrated that left ventricle diastolic function, heart rate recovery index, and coronary flow reserve (coronary microvascular function) are impaired in FMF patients.[3-5] Carotid artery intima media thickness has also been found to be increased in many studies. Hypercoagulability, increased asymmetric dimethylarginine and lipoprotein a levels, increased platelet activation and QT dispersion are other manifestations of the disease in the cardiovascular system.[6-11] In spite of these atherosclerotic risk markers there is no conclusive data showing increased atherosclerotic heart disease prevalence in FMF patients.

Heart-type fatty acid-binding protein (h-FABP) is a low-molecular-weight 14.5-kDa cytoplasmic protein involved in the uptake, transport and metabolism of free fatty acids in myocytes.[12] h-FABP is smaller than cardiac troponin I (cTnI) (25 kDa) and creatine kinase, MB (CK-MB) (87 kDa). As a result of its relatively small size and its primary location in the cytosol rather than in myofibrils, h-FABP is released earlier and in larger amounts into the circulation when membrane integrity is compromised because of myocardial injury.

This marker is extremely specific and sensitive to myocardial ischemia.[13] In addition, h-FABP carries prognostic significance in patients with acute coronary syndromes.[14,15] Recent studies demonstrated that h-FABP levels on admission predict adverse clinical outcomes in acute pulmonary embolism, heart failure and chronic thromboembolic pulmonary hypertension patients.[16-19] Obstructive sleep apnea syndrome has been shown to be associated with increased h-FABP levels as well.[20]

No studies have previously evaluated the h-FABP levels in FMF. As FMF is an autoinflammatory disease with ongoing inflammatory activity and because inflammation plays an important role in the development and progression of atherosclerosis in some rheumatic diseases, we aimed to investigate markers of atherosclerosis in patients with FMF by measuring serum h-FABP and malondialdehyde (MDA) levels.

Abbreviations:

ADMA	*Asymmetrical dimethylarginine*
CRP	*C-reactive protein*
FMF	*Familial Mediterranean fever*
h-FABP	*Heart-type fatty acid-binding protein*
MDA	*Malondialdehyde*
MPV	*Mean platelet volume*
TBARS	*Thiobarbituric acid reactive substances*

PATIENTS AND METHODS

Subjects

Forty consecutive patients with FMF that were age and sex matched and twenty healthy volunteers were selected to form the study population. The diagnosis of FMF was based on Tel-Hashomer criteria. Subjects who had myeloproliferative diseases, malignancies, renal, hepatic and thyroid diseases, immunological diseases, haematocrit <0.30 or >0.52, platelet count <100000/mm^3, patients with acute coronary syndromes, coronary heart disease and those with severe valvular heart diseases were excluded from the study. The permission of a research ethics committee and written informed consent was obtained from all patients before the study.

Blood sampling protocol

Peripheral venous blood samples were obtained following an overnight fasting period. Blood samples were obtained within the first 72 hours of the attack period to search acute attack period. The serum was separated from the cells by centrifugation at 3000 rpm for 10 min and stored at -78 °C until measurement. Blood glucose, lipid parameters, and liver function tests were measured by P800 Roche Hitachi and Olympus AU 5200 automated analyzers. LDL (low density lipoprotein) cholesterol was calculated using the Friedewald formula (LDL= Total Cholesterol-(High density lipoprotein (HDL)+Triglyceride (TG)/5). Complete Blood Count was completed by ROUCHE Sysmex SE 9000 automated analyzer. The serum h-FABP level was measured using an enzyme linked immunosorbent assay kit (HyCult biotechnology b.v, Human hFABP Elisa kit, Uden, Netherlands). The results were expressed as ng/ml. Serum malondi-

aldehyde levels (MDA) were measured by the thiobarbituric acid reactive substances (TBARS) method.[21] MDA, an end product of fatty acid peroxidation, reacts with thiobarbituric acid to form a coloured complex that has maximum absorbance at 532 nm. For this purpose, 0.1 ml of serum was suspended in 1 ml of phosphate buffered saline (pH 6, 100 mmol/l) and then 1 ml of 20% trichloroacetic acid, 1 ml ethyl alcohol (95%) and 1 ml thiobarbituric acid solution (2%) were added. After keeping it in boiling water for 30 min the tube's contents were removed and absorbances were read at 532 nm. MDA concentrations were calculated by comparing the absorbance values of the samples with those of standard MDA solutions. The results were expressed as nmol/ml.

Statistical analysis

Data were analyzed with the software SPSS version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables are presented as mean±SD and categorical variables as frequency and percentage. Student's t-test was used to compare normally distributed continuous variables and the Mann-Whitney U-test for variables without normal distribution. The chi-square test was used to compare categorical variables. Spearman and Pearson correlation analysis was used for correlation analysis. A p-value of <0.05 was considered significant.

RESULTS

Clinical and demographic variables of the groups were summarized in Table 1. The disease was active (attack period) in 11 patients (27.5%), and inactive (attack free period) in 29 patients (72.5%). Several patients (7.5%) were not on colchine treatment, while 75% of patients were taking 1.0-1.5 mg/day of colchine. Sedimentation rate and C-reactive protein (CRP) level were higher in the FMF group compared to the normal group.

The mean h-FABP level in FMF patients was significantly higher than in the normal population (4.9±0.8 *vs.* 3.7±2.1 ng/ml, p<0.01) (Fig. 1a). Mean platelet volume was significantly higher in the FMF group than in the normal group (8.9±0.1 *vs.* 8.2±0.5 fl, p=0.04). Serum MDA levels were the same between the groups (1.9±0.7 *vs.* 1.1±0.3 nmol/ml, p=0.99) (Table 2).

In patients with FMF, disease activity status did not affect the h-FABP and MDA levels (h-FABP: 4.9±0.9 *vs.* 5.0±0.8 ng/ml, p=0.60, MDA: 1.1±0.7 *vs.* 0.1±0.5 nmol/ml, p=0.50, in attack free patients and patients with attack respectively) (Fig. 1b). In addition, WBC, sedimentation rate, CRP level and age of disease onset was different between attack free patients and patients with an acute attack as was expected. WBC,

Table 1. Clinical and demographic variables of groups

	FMF patients (n=40)		Normal (n=20)		*p*
	n (%)	Mean±SD / Median (Range)	n (%)	Mean±SD / Median (Range)	
Male	13 (32.5)		7 (35)		>0.05
Age (years)		30.8±12.2		29.18±10.0	>0.05
Mean age of disease onset (years)		17.1±9.6		–	
White blood cell count (cell/μl)		7253.0±1900.0		6172.0±1008.0	>0.05
Hemoglobin (g/dl)		13.5±1.9		13.0±1.3	>0.05
Platelet count (cell/μl)		259564.0±82319.0		251818.0±32501.0	>0.05
Sedimentation rate (mm/hour)		21.7±14.9		12.4 ±2.6	**0.04**
C-reactive protein level (mg/l)		19.78 (3-241)		2.81 (2-4)	**0.02**
Total cholesterol (mg/dl)		163.2±26.5		167.6±41.7	>0.05
High density lipoprotein (mg/dl)		45.3±7.6		46.6±12.0	>0.05
Triglyceride (mg/dl)		116.4±28.0		119.8±58.8	>0.05
Low density lipoprotein (mg/dl)		108.1±20.0		101.0±33.6	>0.05

FMF: Familial Mediterranean fever.

Table 2. Comparison of h-FABP, mean platelet volume and MDA levels between FMF patients and normal healthy individuals

	FMF patients (n=40) Mean±SD	Normal (n=20) Mean±SD	*p*
h-FABP level (ng/ml)	4.9±0.8	3.1±2.1	**<0.01**
Mean platelet volume (fl)	8.9±0.1	8.2±0.5	**0.04**
MDA level (nmol/ml)	1.1±0.7	1.1±0.3	0.99

h-FABP: Heart-type fatty acid-binding protein; MDA: Malondialdehyde; FMF: Familial Mediterranean fever.

Table 3. Comparison of clinical variables between patients with attack and attack free

	Patients with acute attack Mean±SD / Median (Range)	Attack free patients Mean±SD / Median (Range)	*p*
Mean age of disease onset (years)	25.2±13.1	14.1±5.8	0.00
White blood cell count (cell/μl)	8581±2489	6732±1337	0.00
Sedimentation rate (mm/hour)	35.7±17.9	16.4±9.5	0.00
CRP level (mg/l)	53.9 (3-241)	6.35 (3-36)	0.00
Fibrinogen level (mg/dl)	455±205	328±88	0.00
h-FABP (ng/ml)	5.01±0.79	4.85±0.85	0.60
MDA level (nmol/ml)	0.9±0.50	1.1±0.70	0.50

CRP: C-reactive protein; h-FABP: Heart-type fatty acid-binding protein; MDA: Malondialdehyde; FMF: Familial Mediterranean fever.

sedimentation rate, CRP level and age of disease onset was higher in the active disease group compared to the attack free group (Table 3).

In the correlation analysis, h-FABP and MDA were not related to any clinical or laboratory parameters.

DISCUSSION

To our knowledge, this is the first study evaluating h-FABP level in the FMF disease. In our study, we found that the mean h-FABP level was significantly

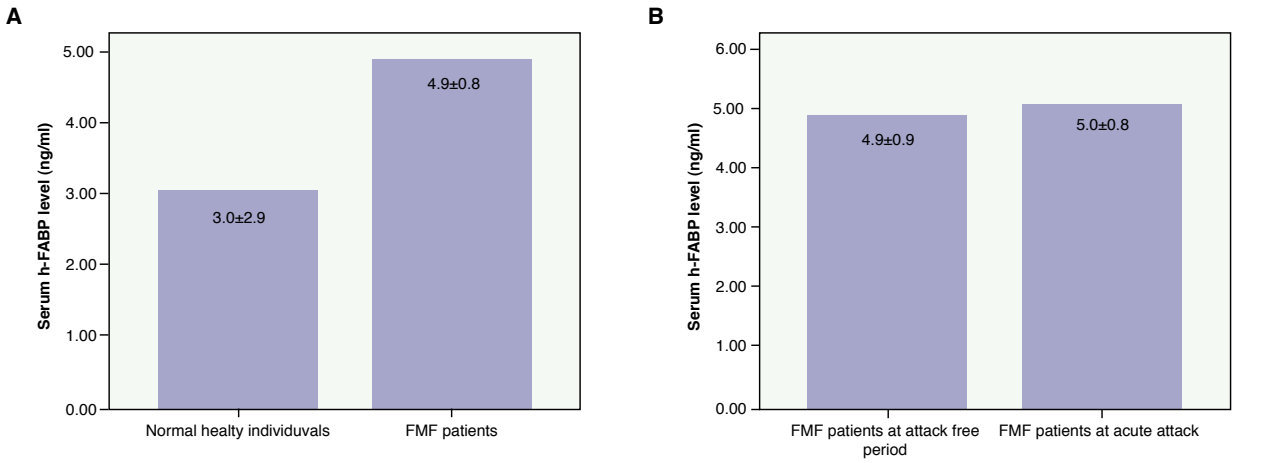

Figure 1. **(A)** Serum h-FFABP levels in healthy individuals and FMF patients. **(B)** Serum h-FFABP levels in FMF patients at the attack free period and acute attack period.

higher in FMF patients compared to normal healthy individuals. Also, mean platelet volume was significantly higher in the FMF group. However, MDA levels were the same between groups. In the subgroup analysis of FMF patients there were no difference in h-FABP and MDA levels between patients with an acute attack and an attack free period. h-FABP and MDA do not seem to be good markers to identify disease activity. h-FABP is a small cytosolic protein and is abundant in cardiac tissue. It is responsible for the intracellular transport of insoluble fatty acids within cells. Its concentration in the plasma of healthy persons is relatively low at 0.3-6 µg/l.[22] h-FABP is an extremely specific and sensitive marker for myocardial ischemia.[13] After myocardial ischemic damage, h-FABP can be detected in the blood within as early as 1 h after the onset of chest pain, with peak values reached at 3-6 h and plasma levels returning to normal within 24-30 h.[23] h-FABP carries prognostic significance in patients with acute coronary syndromes, acute pulmonary embolism, congestive heart failure and chronic thromboembolic pulmonary hypertension patients.[16-19] Obstructive sleep apnea syndrome and metabolic syndrome were found to be associated with increased h-FABP levels.[20,24]

It has been shown that higher disease activity representing higher inflammatory burden is associated with increased morbidity and mortality from cardiovascular disorders in patients with rheumatoid arthritis and systemic lupus erythematosus.[25-28] However, there are conflicting results about cardiovascular risk in FMF. Although FMF presents with exacerbations and attack free periods, it has been demonstrated that there is sustained inflammation during attack-free periods in FMF patients.[1,29] Neutrophils of patients with FMF remain hyperactive during the attack free period due to the sustained overproduction of interleukins and these interleukins exert proatherogenic effects. There are many findings related to the effects of sustained inflammation on the cardiovascular system in FMF. Increased carotid artery intima media thickness and decreased endothelium dependent flow-mediated dilation of the brachial artery have been found in FMF patients in many studies.[6-8] Also, as an expected finding, Bilginer et al.[7] showed a positive correlation between serum amyloid A, fibrinogen level, erythrocyte sedimentation rate and carotid intima media thickness. This result supports the idea that acute phase response and increased inflammation begets atherosclerotic lesion development. Contrary to these studies, Sarı et al.[30] reported that carotid artery intima media thickness and endothelium dependent flow-mediated dilation did not change in FMF patients compared to healthy controls. However, studies indicating the positive relationship between carotid intima media thickness and FMF seem to have more support. Although preclinical atherosclerosis is more prevalent in FMF, clinical atherosclerotic heart disease prevalence was reported to be significantly lower than normal controls in Israel.[31] This unexpected finding was interpreted as a consequence of colchicine treatment by Langevitz et al.[31] We may say that increased subclinical atherosclerotic propensity can not reach the clinical level, perhaps due to successful colchicine therapy.

There are many other effects of FMF on the cardiovascular system other than atherosclerosis. Researchers demonstrated impaired left ventricle diastolic function in this disease.[3,4] Sarı et al.[32] reported deteriorated right ventricle function in FMF patients. In addition, the cardiac autonomic system is affected in FMF. Heart rate recovery index is also impaired in patients with FMF compared to control subjects, indicating the unbalanced sympathetic system overdrive during the disease.[5] Coronary flow reserve was found to be significantly lower in FMF patients. Decreased coronary flow reserve in this disease is an indicator of impaired coronary microvascular function. Interestingly deterioration in coronary flow reserve correlated with hs-CRP level, supporting the importance of inflammation on cardiac involvement.[3] Elevated levels of asymmetrical dimethylarginine (ADMA) in FMF is thought to be another index of endothelial dysfunction. ADMA levels were higher during the attack period than during the attack free period, telling us how inflammation mediated impairment of the endothelium functions during an attack.[9] Shortened prothrombin time and thrombin time, decreased protein C activity and elevation of prothrombin fragment F1+2 are found in FMF patients. These changes in hemostatic parameters points to the hypercoagulable state in FMF even during the attack-free period.[10]

Increased platelet activity is one of the most commonly blamed mechanisms in atherosclerosis pathogenesis. Mean platelet volume (MPV) is a parameter of platelet size. Large platelets that contain more dense granules are metabolically more active than small

platelets and they are more thrombogenic than smaller ones.[33-35] They also have higher levels of procoagulatory surface proteins, such as P-selectin, glycoprotein IIIa and produce more prothrombotic factors like thromboxane B2, seratonin and ß-thromboglobulin.[36,37] As MPV increases the inhibitory effect of prostacyclin (PGI2) decreases. MPV is increased in patients with acute myocardial infarction, stroke, diabetes mellitus, congestive heart failure and hypertensive patients with evidence of target organ damage.[38-40] These findings support the idea that larger platelets with increased MPV show greater thrombogenic activity and prothrombotic state. Reactive oxygen species are highly reactive molecules that, when present in excess, overwhelm the protective systems and result in cell damage and lipid peroxidation. Further, decomposition of peroxidized lipid yields a wide variety of end-products, including malondialdehyde (MDA). Lipid peroxidation is a well-established mechanism of cellular injury in humans, and is used as an indicator of oxidative stress in cells and tissues.

Our study supports the idea of increased atherosclerotic burden and thrombogenic activity in FMF patients. Both increased h-FABP and MPV confirm these findings. On the other hand these results can not solely be attributed to the increased oxidative stress in the disease state. MDA was the same between normal individuals and FMF patients. FMF may be thought as a risk factor for atherosclerosis and strict risk factor modification can be managed to prevent the atherosclerotic disease.

In conclusion, to our knowledge, the present study is the first case-control study in which significant alterations in serum h-FABP levels were detected in patients with FMF. Further studies are required to investigate the relationship between the values of h-FABP and the development of cardiac disorders in patients with FMF.

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Key words: Acute disease; atherosclerosis/blood; biological markers/blood; fatty acid-binding proteins; familial Mediterranean fever/complications; malondialdehyde.

Anahtar sözcükler: Akut hastalık; ateroskleroz/kan; biyolojik belirteç/kan; yağ asidi bağlayıcı protein; ailevi Akdeniz ateşi/komplikasyonlar; malondialdehit.