Apelin and fetuin-a may be subclinical inflammation biomarker in familial mediterranean fever: A pilot study

Ailevi akdeniz ateşinde apelin ve fetuin-a subklinik inflamasyonun biyobelirteci olabilir: Bir pilot çalışma

Ali Şahin[1], Özlem Demirpençe[2], Mehtap Şahin[2], Gökhan Bağcı[2], Doğan Seven[3], Halef Okan Doğan[2], Ayşe Camcı[1], Mehmet Emin Derin[1], Binnur Bağcı[4]
[1]Department of Internal Medicine - Rheumatology, Faculty of Medicine,
[2]Department of Biochemistry, Faculty of Medicine, [3]Department of Internal Medicine, Faculty of Medicine,
[4]Department of Nutrition and Dietetics, Faculty of Health Sciences, Cumhuriyet University, Sivas, Turkey

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Öz

Amaç: Pozitif akut faz reaktanları genellikle ailevi Akdeniz ateşinin (AAA) atak döneminde (AD) yükselir ve atak-dışı dönemde (ADD) normal seviyelerine döner. Bazı hastalarda, bu akut faz reaktanlarının seviyesi ADD de düşmez, bu bize ADD de subklinik vasküler inflamasyonun devam ettiğini gösterir. Bu bilgi doğrultusunda, AAA hastalarında ADD de apelin ve fetuin-a'nın inflamatuvar biyobelirteçolarak kullanılıp kullanılamayacağını araştırdık. Gereç ve Yöntem: 30 AAA hastası ADD de ve 30 sağlıklı birey çalışmaya alındı. Serum apelin ve fetuin-a seviyeleri ELİSA yöntemi ile ölçüldü. Bulgular: AAA'lı hastalarda ortanca apelin seviyesi 113.07±15.9 ng/L ve sağlıklı bireylerde 307.82±52.76 ng/L idi (p= 0.002). Ortanca fetuin-a seviyesi AAA grubunda 1352.2±127.61 ng/mL ve kontrol grubunda 843.82±137.66 ng/mL idi (p= 0.009). AAA hastalarında, apelin ve fetuin-a seviyeleri arasında anlamlı bir ilişki saptandı (r = 0.399; p = 0.029). Ayrıca, yaş ve apelin arasında anlamlı ters bir ilişki (r= -0.499; p = 0.005), ve beden kitle indeksi (BKİ) ve apelin arasında pozitif bir ilişki (r = 0.769; p = 0.001) saptandı. İlave olarak, BKİ ve fetuin-a arasında anlamlı ilişki saptandı (r = 0.397; p = 0.030). Tartışma: AAA'lı hastalarda ADD de subklinik vasküler inflamasyonun devam ettiğinin göstergeci olarak, düşük serum apelin seviyeleri ve yüksek fetuin-a seviyeleri sağlıklı bireylere kıyasla gözlendi. AAA'ya bağlı subklinik inflamasyonu göstermede apelin ve fetuin-a'nın rolünü saptamada daha popülasyonlu ve farklı etnik grupları içeren çalışmlara ihtiyaç vardır.

Anahtar Kelimeler

Apelin; Ailevi Akdeniz Ateşi; Biyobelirteç; Fetuin-A; Subklinik İnflamasyon

Abstract

Aim: Positive acute-phase reactants generally increase during the attack period (AP) of familial Mediterranean fever (FMF) and return to normal range in the attack-free period (AFP). In some patients, the level of these acute-phase reactants does not decrease during the AFP, suggesting that subclinical vascular inflammation continues during the AFP. In the context of this information, we tested whether apelin and fetuin-A can be used as inflammatory biomarkers in the AFP of FMF patients. Material and Method: Thirty FMF patients within AFP and thirty healthy subjects were included in this study. Serum apelin and fetuin-a levels were measured using enzyme-linked immunosorbent assay (ELISA) method. Results: The median levels of apelin were 113.07±15.9 ng/L in FMF and 307.82±52.76 ng/L in healthy subjects (p= 0.002). The median levels of fetuin-A were 1352.2±127.61 ng/mL in the FMF group and 843.82±137.66 ng/mL in the control group (p= 0.009). In FMF patients, there was a significant correlation between apelin and fetuin-A levels (r = 0.399; p = 0.029). Furthermore, a significant inverse correlation was found between age and apelin (r= -0.499; p = 0.005), and a significant positive correlation was found between BMI and apelin (r = 0.769; p = 0.001). Additionally, a significant correlation was found between BMI and fetuin-A (r = 0.397; p = 0.030). Discussion: Lower serum apelin levels and higher fetuin-A levels were observed in FMF patients with AFP than in healthy subjects, suggesting that subclinical vascular inflammation continues during AFP in patients with FMF. Further studies with large study populations and different ethnic groups are necessary to show the role of apelin and fetuin-A in subclinical inflammation resulting from FMF.

Keywords

Apelin; Biomarkers; Familial Mediterranean Fever; Fetuin-A; Subclinical Inflammation

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Corresponding Author: Ali Sahin, Department of Internal Medicine, Rheumatology, Faculty of Medicine, Cumhuriyet University, 58140, Sivas, Turkey.
T.: +90 3462580949 E-Mail: dralsahin@hotmail.com

Introduction

Familial Mediterranean fever (FMF) (OMIM 249100) is an auto-inflammatory disorder that shows an autosomal recessive inheritance pattern. The disease is characterized by recurrent fever attacks accompanied by abdominal pain, chest pain or joint pain, myalgia, and erysipelas-like skin lesions [1]. FMF predominantly affects Middle Eastern populations surrounding the eastern Mediterranean region, including Armenians, Arabs, Turks, and non-Ashkenazi Jews [2]. The mutations in the MEFV gene are responsible for FMF disease. The MEFV gene is located on chromosome 16p13.3; product of this gene, a 781 amino acids long protein, is termed pyrin/marenostrin [3].

The attacks of FMF are self-limited, lasting 1-3 days, and patients are usually symptom-free between the attack episodes. Positive acute-phase reactants including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and serum amyloid A (SAA) increase in the attack periods (APs) of FMF, and usually return to normal range in attack-free periods (AFPs). It has been reported that subclinical inflammation may continue even during the AFP of FMF [4,5]. Colchicine treatment commonly is utilized in the management of the attacks of FMF and in prevention of complications associated with inflammation, such as amyloidosis [6,7].

Apelin is an adipokine produced by adipocytes and a ligand of the G-protein coupled apelin receptor (APJ) [8]. In the human body, APJ is expressed by the heart, lung, liver, kidney, gastrointestinal tract, brain, adipose tissue, adrenal glands, endothelium, and plasma cells [9]. Considering the fact that apelin stimulates nitric oxide release and triggers arterial vasodilation, it is considered a potential biomarker for cardiovascular disease risk assessment. Moreover, insulin directly upregulates the expression of apelin, making this adipokine an attractive candidate protein marker for metabolic disorders such as diabetes mellitus (DM). Furthermore, low apelin levels have been found to be associated with elevated LDL levels [10] and also with VCAM-1 and E-selectin, the biomarkers of endothelial cell activation. The biomarkers have previously been found to be correlated with apelin levels [11]. Apelin level is increased by some pro-inflammatory cytokines such as TNF-α in metabolic, autoimmune, and inflammatory conditions [12]. Recently, apelin levels have also been measured in some rheumatic diseases, such as rheumatoid arthritis (RA) [13] and ankylosing spondylitis (AS) [14].

Fetuin-A is a protein secreted by the liver, kidney, bone, brain, lungs, and the cardiovascular system [15]. Fetuin-A is implicated in several diverse functions, including response to systemic inflammation, regulation of insulin and hepatocyte growth factor receptors, and bone resorption and osteogenesis [16]. Fetuin-A is known as a negative acute-phase reactant because of its decreased level in acute and chronic inflammation [17]. Fetuin-A levels were found to be decreased in certain rheumatic diseases including RA [18,19], osteoarthritis [15], and AS [20]. It has been suggested that fetuin-A can be a novel inflammatory biomarker in FMF [21].

As far as we know, there is no study investigating the role of apelin in the pathogenesis of FMF and only one study has been conducted in FMF patients for fetuin-A [21]. In light of this, we aimed to evaluate the serum apelin and fetuin-A levels in patients with FMF during AFP and to investigate their correlation with demographic and biochemical parameters.

Material and Method

Clinical Research Ethics Committee of Cumhuriyet University approved the study protocol. Before enrollment, a written informed consent was obtained from all participants. A total of thirty FMF patients during AFP who fulfilled the Tel Hashomer criteria were included in this study. For the control group, thirty age-, sex-, and body mass index (BMI)-matched healthy individuals were included in the study. Following an overnight fast, the blood samples of subjects were obtained in the morning (8:00-9:00) for the measurement of laboratory tests. The hemogram, ESR, CRP, fibrinogen, serum creatinine, uric acid, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using standard procedures in the venous blood samples. Demographic characteristics including age, BMI, and disease duration were recorded. The MEFV gene profiles of the FMF patients were obtained from hospital file records.

Measurement of serum apelin and fetuin-A levels by ELISA

A total of 7.5 mL of venous blood samples obtained from the FMF patient and control subjects were collected into a serum collection tube. These samples were centrifuged at 3000 rpm for 10 min and obtained serums were portioned. Serum samples were immediately stored at -80ºC until the measurement time. Serum samples were defrosted for the quantitative measurement of serum apelin and fetuin-A levels; commercial enzyme-linked immunosorbent assay (ELISA) kits were used.

Statistical analysis

All tests were performed using SPSS version 22.0 (SPSS IBM, Armonk, NY, USA). All demographic and quantitative data were shown as mean ± standard deviation and median (min-max). Kolmogorov-Smirnov test was used for normality assumption of continuous variables. Student's t-test or Mann-Whitney U-test was used for the comparison between groups of continuous variables. Correlations between variables were analyzed using Pearson's or Spearman's rank correlation coefficients. A p value less than 0.05 was accepted as statistically significant and all results were expressed with a 95% confidence interval.

Results

The present study consists of 30 FMF patients in AFP and 30 healthy controls. The mean ages of patients and control subjects were 29.7±10.9 and 34.3±9.6, respectively. BMI was 26.4±3.6 for patients and 27.0±3.1 for controls. There is no statistically significant difference between patients and controls in terms of age and BMI ($p > 0.05$). Of the FMF patients and controls, 20 (66.7%) were female and 10 (33.3%) were male. Mean disease duration was 9.2±7.9 years in the FMF patients. Laboratory findings of patients with FMF and control subjects are reported in Table 1.

The distribution of MEFV gene mutation frequencies in the FMF patients was as follows: no mutation in 4 (13.3%) patients, M694V heterozygous in 7 (23.3%), M694V homozygous in 3 (10%), E148Q heterozygous in 5 (16.7%), M680I (G/C) heterozygous in 2 (6.7%), M680I (G/C) homozygous in 1 (3.3%), V726A heterozygous in 2 (6.7%), and compound heterozygous mutation in 6 (20%) cases.

Figure 1 shows serum apelin and fetuin-A levels in FMF patients and controls. The median levels of apelin were 307.82±52.76 ng/L in healthy subjects and 113.07±15.9 ng/L in FMF patients (p= 0.002) (Figure 1). The median levels of fetuin-A were 843.82±137.66 mg/L in the control group and 1352.2±127.61 mg/L in the FMF group (p = 0.009) (Figure 1).

Table 2 shows the correlations between apelin, fetuin-A, and demographic and biochemical parameters. Significant correlation was found between apelin and fetuin-A levels (r = 0.399; p = 0.029). There was a significant inverse correlation between apelin and age (r= -0.499; p = 0.005) and a strong significant positive correlation was detected between apelin and BMI (r = 0.769; p = 0.001). The correlations between apelin and the other parameters were not significant. Fetuin-A was found to be correlated with BMI (r = 0.397; p = 0.030). The correlations between fetuin-A and the other demographic and biochemical characteristics were not significant.

Discussion

In the current study, we evaluated the serum apelin and fetuin-A levels in patients with FMF in AFP and compared with healthy subjects. The median levels of apelin were lower and median fetuin-A levels were higher in FMF patients compared with controls. In the FMF patients, there was a statistically significant correlation between apelin and fetuin-A levels. There was a significant inverse correlation between apelin and age, and a strong significant positive correlation was detected between apelin and BMI. Moreover, fetuin-A has been found to be correlated with BMI. We suggest that apelin and fetuin-A may be independent predictors of subclinical vascular inflammation continued during AFP in patients with FMF.

In clinical practice, developments in biomarker discovery provide important chances for the diagnosis and disease follow-up. Many biomarkers of inflammation are used by clinicians for predicting disease process, understanding disease mechanisms, recognizing, and monitoring a particular disease [22]. The implication of these biomarkers in the pathogenesis of inflammatory diseases is also a potential field of interest. Positive acute-phase reactants generally increase during the AP of FMF and return to normal range in AFP. In some patients, the levels of these acute-phase reactants do not decrease during AFP, suggesting that subclinical vascular inflammation continues during AFP [23]. In the context of this information, we tested whether apelin and fetuin-A can be used as inflammatory biomarkers in AFP of FMF patients.

There are a limited number of studies regarding fetuin-A and apelin in inflammatory rheumatic diseases. In the only study conducted with familial Mediterranean fever patients, Oncu et al [21]. measured serum levels of fetuin-A during AFP, 12 hours after an attack, and 7 days after an attack. They detected a decrease in the serum fetuin-A levels in AFP compared to 12 hours after AP. Additionally, they observed that fetuin-A was inversely correlated with positive acute-phase reactants such as CRP, ESR, fibrinogen, WBC, and ceruloplasmin. Similarly, lower serum levels of fetuin-A were reported by Saroha et al. [18] in RA patients. They asserted that low fetuin-A levels in RA patients might have resulted from the chronic inflammation developing in association with inflammatory activity and malnutrition. However, they found no correlation with clinical parameters. Sato et al.[19] reported low levels of serum fetuin-A in RA patients and found inverse correlation between fetuin-A and two positive acute-phase reactants: ESR and CRP. They also reported that fetuin-A was positively correlated with albumin, total cholesterol, and hemoglobin. Gökmen et al.[20] detected lower serum levels of fetuin-A in the AS patients compared to the control subjects. They found an inverse correlation

Table 1. Laboratory findings of patients with familial Mediterranean fever.

Variables	Patients (n=30)	Min-max
Erythrocyte sedimentation rate (mm/h)	22.9±21.7	(4-79)
C-reactive protein (mg/L)	34.2±51.8	(1-173)
Fibrinogen (mg/dL)	392.2±147.6	(233-841)
White blood cell count (10^9/L)	7.1±1.9	(4.11-10.7)
Neutrophil count (10^9/L)	4.8±1.8	(2.3-9.4)
Lymphocyte conut (10^9/L)	1.7±0.5	(0.4-2.8)
Erythrocyte count (10^{12}/L)	4.8±0.5	(4.0-5.93)
Hemoglobin (g/dL)	14.0±1.6	(10.8-17.6)
Platelet count (10^3/µl)	266.3±78.4	(154-565)
Creatinine (mg/dL)	0.65±0.17	(0.4-1.27)
Uric acid (mg/dL)	4.3±1.2	(1.9-6.7)
Alanine aminotransferase (U/L)	32.1±46.5	(10-265)
Aspartate aminotransferase (U/L)	28.2±26.6	(15-161)

Data were given mean±SD and min-max

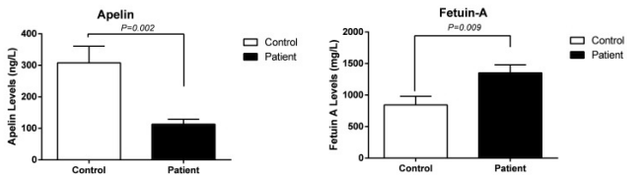


Figure 1. Serum levels of fetuin-A and apelin in FMF patients and healthy control subjects. The median levels of apelin were 307.82±52.76 ng/mL in healthy controls and 113.07±15.9 ng/mL in FMF patients (p = 0.002). The median levels of fetuin-A were 843.82±137.66 ng/mL in the control group and 1352.2±127.61 ng/mL in the FMF group (p = 0.009).

Table 2. Correlation between and serum levels of apelin, fetuin-A and laboratory findings in patients with Familial Mediterranean fever

Variables	Apelin		Fetuin-A	
	r	p	r	p
Fetuin-A	0.399	0.029	-	-
Age	-0.499	0.005	-0.144	0.448
Body mass index	0.769	0.001	0.397	0.030
Disease duration	-0.215	0.254	-0.066	0.727
Erythrocyte sedimentation rate	0.031	0.871	0.133	0.482
C-reactive protein	0.084	0.657	0.252	0.179
Fibrinogen	0.200	0.289	0.128	0.501
White blood cell count	0.143	0.452	-0.036	0.851
Hemoglobin	-0.319	0.086	-0.076	0.690
Platelet count	-0.208	0.270	0.0130	0.945
Creatinine	-0.181	0.339	-0.082	0.667
Alanine aminotransferase	-0.235	0.212	-0.135	0.476
Aspartate aminotransferase	-0.180	0.342	-0.194	0.305
Uric acid	-0.034	0.859	0.280	0.134

between CRP and fetuin-A levels. However, they found no correlation between fetuin-A and clinical parameters. In contrast, Sari et al.[24] found significantly higher fetuin-A levels in AS patients. Similarly, Tuylu et al.[25] found significantly higher fetuin-A levels in AS patients with syndesmophytes compared to those without syndesmophytes and healthy controls. Additionally, Harman et al.[26] found significantly high serum fetuin-A concentrations in the axial SpA and RA patients; however, serum levels of fetuin-A were not found to be different in the peripheral SpA patients and healthy subjects. They also observed significant correlations between fetuin-A and the clinical parameters of the axial SpA patients.

In early-stage RA (ERA) patients, Di Franco et al.[13] measured serum levels of apelin before and after disease-modifying antirheumatic drug therapy; they also measured intima-media thickness (IMT). They found decreased serum apelin levels in the ERA group, but serum apelin levels were not altered by treatment. However, IMT did not show significant changes. In non-diabetic patients with AS on treatment with infliximab, Genre et al.[14] showed that serum levels of apelin did not correlate with disease activity or metabolic syndrome. Topsakal et al.[27] investigated serum apelin and fetuin-A levels and assessed their associations with carotid intima-media thickness (CIMT) in patients with acromegaly. They found that serum levels of these proteins increased in patients with acromegaly. They found significant correlation between apelin and fetuin-A. Additionally, CIMT values were similar between acromegaly patients and controls. In the present study, we measured higher serum fetuin-A and lower apelin levels in FMF patients during AFP than in healthy controls.

Endothelial dysfunction and CIMT are used to define preclinical atherosclerosis and they are usually associated with systemic inflammatory and autoimmune diseases. Patients with inflammatory diseases such as RA and systemic lupus erythematosus are considered to have an increased risk of atherosclerotic cardiovascular complications[13,28,29]. In various studies, CIMT was measured in FMF patients, and a significant increase was observed[29-33]. In patients with Behcet's disease, Uyar et al.[28] found significantly high CIMT and coronary artery calcium scoring (CACS) and high serum fetuin-A levels compared to controls. They also observed significant correlations between serum levels of fetuin-A and CIMT and between fetuin-A levels and CACS. Turkmen et al.[34] found that serum levels of fetuin-A were inversely correlated with CACS in hemodialysis patients. They suggested that fetuin-A may play a role in increased mortality via accelerating coronary artery calcification. A significant inverse correlation was found between serum fetuin-A level and CIMT in hemodialysis patients[35]. Fetuin-A has an important role in the inhibition of insulin receptor signaling and calcification[36]. It has been suggested that high serum levels of fetuin-A may accelerate atherosclerosis, and fetuin-A and CIMT exhibit positive correlation in patients with DM[37]. Similarly, in adolescent type 1 diabetic patients, high levels of fetuin-A and increased CIMT have been found[38]. Increased CIMT is the early sign of atherosclerosis. For this reason, we think that the possible association between CIMT and fetuin-A and also apelin need to be investigated.

MEFV mutations have great importance in assessment of the severity of FMF[2,4]. In patients with FMF, homozygote M694V mutation was found to be associated with a clinically more severe course of disease, and patients carrying M694V mutation have a higher risk for amyloidosis development[4,39]. Although E148Q mutation in heterozygous state is predominantly considered to be a non-amyloidosis causing mutation, in a recent study heterozygous E148Q mutation was detected in 3 of 61 secondary (AA) amyloidosis patients[40]. In our study, ten patients had M694V, three patients had M680I (G/C), two patients had V726A, six patients had compound heterozygous mutations, and five patients had E148Q mutation; four patients had no MEFV mutations. As shown above, E148Q mutation is common in patients with FMF. For this reason, the development risk of amyloidosis in patients bearing E148Q mutation should not be ignored. The frequency of carriers of MEFV mutation is approximately 20-30% in populations who live in regions surrounding the eastern Mediterranean[1]. Subclinical inflammation was not only found in FMF patients but also was shown in patients carrying MEFV mutations [4]. When detecting amyloidosis in FMF patients, the role of CIMT and impaired endothelial function should be investigated deeply.

In conclusion, the low serum apelin and high fetuin-A levels in FMF patients in AFP compared to healthy subjects suggest that subclinical vascular inflammation continues during AFP in patients with FMF. The relatively small sample size was a major limitation of the current study. The second limitation was that we did not measure serum apelin and fetuin-A concentrations during the APs of FMF. Additionally, CIMT measurements of FMF patients were not performed in the current study. Further studies with large study populations and different ethnic groups, measuring the serum apelin and fetuin-A levels both in AP and in AFP of FMF patients, and measuring CIMT value of FMF patients. are necessary to show the role of apelin and fetuin-A in subclinical inflammation resulting from FMF.

Competing interests

The authors declare that they have no competing interests.

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