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ORIGINAL ARTICLE

Lipid profile and atherogenic indices and their association with platelet indices in familial Mediterranean fever

Ailevi Akdeniz ateşi'nde lipit profili ve aterojenik indeks düzeyleri ve bunların trombosit indeksleri ile ilişkisi

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ABSTRACT

Objective: The aim of this study was to investigate lipid profiles and atherogenic indices and their association with platelet indices in Familial Mediterranean Fever (FMF) patients.

Methods: A total of 63 FMF patients and 51 healthy individuals were included in this retrospective study. Inflammatory marker values (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] and fibrinogen), platelet indices (mean platelet volume, plateletcrit value, platelet large cell ratio, and platelet distribution width), lipid profiles (levels of total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein cholesterol) were recorded. Atherogenic indices (atherogenic index of plasma [AIP], atherogenic coefficient [AC], Castelli's risk indices I and II [CRI I and II]) were calculated using lipid parameters.

Results: In FMF patients, while AIP, AC, and CRI I and II values were significantly higher than in the healthy control group, the HDL cholesterol level was significantly lower (all $p<0.05$). However, no significant difference was determined in terms of the other studied parameters (all $p>0.05$). In male FMF patients, whereas AIP, AC, and CRI I and II values were significantly higher than in female FMF patients, the platelet count, ESR, and HDL cholesterol levels were significantly lower (all $p<0.05$). The level of CRP was negatively correlated with HDL cholesterol ($r=-0.275$; $p=0.032$) and total cholesterol level ($r=-0.313$; $p=0.014$) in FMF patients. HDL cholesterol level was negatively correlated with disease duration ($r=-0.269$; $p=0.049$).

Conclusion: The use of atherogenic indices may be recommended to identify patients with an increased risk of atherosclerotic cardiovascular disease in FMF, especially in male patients.

ÖZET

Amaç: Bu çalışmada, Ailevi Akdeniz Ateşi (AAA) hastalarında lipit profili ve aterojenik indeks düzeylerini ve bunların trombosit indeksleri ile olan ilişkisini araştırmayı amaçladık.

Yöntemler: Bu geriye dönük çalışmaya AAA'lı 63 hasta ve sağlıklı 51 birey dahil edildi. Enflamatuvar belirteçlerin (eritrosit sedimantasyon hızı [ESR], C-reaktif protein [CRP] ve fibrinojen), trombosit indekslerinin (ortalama trombosit hacmi, trombosit krit, büyük trombosit oranı ve trombosit dağılım genişliği) ve lipit parametrelerinin (toplam kolesterol, trigliserit, düşük yoğunluklu lipoprotein kolesterol ve yüksek yoğunluklu lipoprotein kolesterol) düzeyleri kaydedildi. Ayrıca, aterojenik indeksler (plazma aterojenik indeksi [AIP], aterojenik katsayı [AK], Castelli risk indeksleri I ve II [CRI-I ve II]) lipit parametreleri kullanılarak hesaplandı.

Bulgular: AAA'lı hastalarda AIP, AK, CRI-I ve II düzeyleri sağlıklı kontrol grubuna göre anlamlı derecede yüksek iken, yüksek yoğunluklu lipoprotein kolesterol düzeyi anlamlı derecede düşüktü ($p<0.05$). Bununla birlikte, diğer incelenen parametreler açısından anlamlı bir fark tespit edilmedi ($p>0.05$). AAA'lı erkek hastalarda AIP, AK, CRI-I ve II düzeyleri kadın hastalara göre anlamlı derecede yüksek iken, trombosit, ESR ve yüksek yoğunluklu lipoprotein kolesterol düzeyleri anlamlı derecede düşüktü ($p<0.05$). AAA'lı hastalarda CRP düzeyi ile yüksek yoğunluklu lipoprotein kolesterol ve toplam kolesterol düzeyleri arasında negatif korelasyon bulundu (sırasıyla, $r=-0.275$, $p=0.032$ ve $r=-0.313$, $p=0.014$). Ayrıca, yüksek yoğunluklu lipoprotein kolesterol düzeyi ile hastalık süresi arasında negatif korelasyon saptandı ($r=-0.269$, $p=0.049$).

Sonuç: AAA'da özellikle erkek hastalarda, artmış aterosklerotik kardiyovasküler hastalık riskinin belirlenmesi için aterojenik indekslerin kullanımı önerilebilir.

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Familial Mediterranean fever (FMF) is a chronic inflammatory disease that is the result of a mutation of the MEFV gene. The MEFV gene encodes the protein pyrin/marenostrin, which is thought to play a role in inflammatory pathways. Mutation of the MEFV gene leads to a loss of pyrin function and results in uncontrolled inflammation.[1,2] Inflammation in FMF disease is important in the onset and the progression of atherosclerotic cardiovascular disease, as it causes functional changes in microcirculation.[3–5]

Abbreviations:

AC	*Atherogenic coefficient*
AIP	*Atherogenic index of plasma*
CRI	*Castelli's risk index*
CRP	*C-reactive protein*
ESR	*Erythrocyte sedimentation rate*
FMF	*Familial Mediterranean Fever*
HDLc	*High-density lipoprotein cholesterol*
LDLc	*Low-density lipoprotein cholesterol*
MPV	*Mean platelet volume*
PCT	*Plateletcrit*
PDW	*Platelet distribution width*
P-LCR	*Platelet large cell ratio*
TC	*Total cholesterol*
TG	*Triglycerides*

It has been reported that increased platelet activation is related to the cardiovascular risk factors that expedite atherogenesis.[6,7] Platelet indices, including platelet large cell ratio (P-LCR), mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW), are platelet activation indicators.[8] Of these parameters, the MPV level, in particular, has been said to be elevated in cardiovascular diseases, such as hypertrophic cardiomyopathy,[9] acute myocardial infarction,[10] and pulmonary arterial hypertension.[11]

Traditionally, the atherogenic lipid profile consists of an increased level of total cholesterol (TC), low-density lipoprotein cholesterol (LDLc), and triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDLc). Currently, Castelli's risk indices I and II (TC/HDLc and LDLc/HDLc, respectively), the atherogenic index of plasma (AIP; Log TG/HDLc), non-HDLc (TC-HDLc), and the atherogenic coefficient (AC; Non-HDLc/HDLc) parameters are used for a better prognosis in cases of atherosclerosis and cardiovascular disease.[12–15]

The objective of this study was to investigate the lipid profile and atherogenic indices in FMF patients and to assess the association with platelet indices.

METHODS

The records of adult patients diagnosed with FMF between June 2014 and December 2015 in the department of the internal medicine were reviewed retrospectively. In all, 63 FMF patients and 51 healthy controls were included in the study. All of the patients were diagnosed with FMF based on the Tel Hashomer criteria[16] and were taking colchicine.

Individuals who had cardiovascular disease, hematological disorders, other rheumatological diseases, cancer, diabetes, take medication other than colchicine, smoke, or drink alcohol were not included in the study. Approval for this study was received from the local ethics committee.

Laboratory analysis

Ethylenediaminetetraacetic acid tubes were used for a complete blood count analysis. The complete blood count parameters were analyzed in a Sysmex XN-1000 analyzer (Sysmex Corp., Kobe Japan) within 2 hours to prevent platelet swelling. The other study test samples were analyzed according to classic methods using various analyzers: the CRP level was assessed with Siemens' BN II nephelometer (Siemens Healthineers, GmbH, Erlangen, Germany) ESR with the Test-1 automated analyzer (Alifax S.p.A. Polverara. Italy), fibrinogen level with an STA Compact coagulation analyzer (Diagnostica Stago, Inc., Parsippany, NJ, USA) and TC, HDLc, LDLc, and TG levels were measured with the Abbott Architect c8000 (Abbot Diagnostics, Inc., Lake Forest, IL, USA). The indices used in this study were calculated as follows: CRI-I=(TC/HDLc),[12] CRI-II=(LDLc/HDLc),[12] AIP=(log TG/HDLc),[13] non-HDLc=(TC–HDLc),[14] and AC=(non-HDLc/HDLc).[15]

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp., Armonk, NY, USA). Normal distribution was determined using the Kolmogorov-Smirnov test. Student's t-test was used to compare the data expressing a normal distribution; otherwise, the Mann-Whitney U test was used. A chi-square test was used to compare categorical variables. Normally distributed continuous variables were reported as mean±SD, and those non-normally distributed were reported as median (min-max).

Categorical variables were reported as number and percent. Pearson's and Spearman's correlation methods were applied for relationship analysis. P values equal to or less than 0.05 were accepted as statistically significant.

RESULTS

The demographic characteristics and laboratory findings of the FMF patients and healthy controls are summarized in Table 1. The AIP, AC, CRI-I and II values were significantly higher and the HDLc levels were significantly lower in the FMF patients compared with the healthy controls. However, there was no significant difference between the FMF patients and healthy controls in terms of age, gender distribution, TC, LDLc, TG, P-LCR, MPV, PCT, or PDW levels (Table 1).

When FMF patients were examined as separate groups according to gender, the AIP, AC, and CRI-I and II values were significantly higher, and the platelet count, ESR, and HDLc levels were significantly lower in male FMF patients compared with the female patients. The other parameters were similar between the 2 groups (Table 2).

The TC, TG, HDLc, and LDLc levels of patients using colchicine in a dose of less than or equal to 1mg and more than 1mg were compared. There was no significant difference between the 2 groups in terms of these parameters (p=0.218, p=0.910, p=0.133, and p=0.255, respectively).

The correlation of lipid profile and atherogenic indices with the other parameters studied in FMF patients is provided in Table 3. The CRP level was negatively correlated with HDLc (r=–0.275; p=0.032) and TC levels (r=–0.313; p=0.014) (Figs. 1 and 2). Furthermore, the HDLc level was negatively correlated with disease duration (r=–0.269; p=0.049) (Fig. 3).

DISCUSSION

FMF is a chronic inflammatory disease that is characterized by episodes of attack and attack-free periods. Subclinical inflammation can continue between

Table 1. Characteristics and laboratory parameters of the study groups

	FMF (n=63)	Control (n=51)	p
Age (years)	29 (18–45)	28 (18–50)	0.923*
Gender (male), n (%)	34 (54)	28 (54.9)	0.921†
Platelet ($10^3/\mu L$)	258 (150–627)	270 (172–548)	0.949*
Platelet distribution width (fL)	13±1.9	12.5±1.9	0.186‡
Mean platelet volume (fL)	10.8±0.8	10.5±0.9	0.169‡
Plateletcrit (%)	0.28 (0.16–0.62)	0.29 (0.18–0.54)	0.869*
Platelet large cell ratio (%)	31.1±6.3	29.4±7.1	0.168‡
Low-density lipoprotein cholesterol (mg/dL)	117.5±36.7	111.6±22.6	0.474‡
High-density lipoprotein cholesterol (mg/dL)	40.5 (19.7–75.1)	47.7 (36.3–76.4)	<0.001*
Total cholesterol (mg/dL)	178.8 (112.1–286.9)	181.6 (144.7–239.8)	0.761*
Triglyceride (mg/dL)	96 (39.2–435.5)	92.1 (37.2–224.8)	0.325*
Non-High-density lipoprotein cholesterol	134.9 (70.1–243)	128 (84.6–198.7)	0.365*
Castelli's risk index I	4.4 (2.7–11.5)	3.7 (2.4–5.9)	<0.001*
Castelli's risk index II	2.9 (1.4–8.1)	2.3 (1.1–4.5)	0.004*
Atherogenic coefficient	3.4 (1.7–10.5)	2.7 (1.4–4.9)	<0.001*
Atherogenic index of plasma	0.43±0.32	0.28±0.26	0.004‡
Erythrocyte sedimentation rate (mm/h)	15 (2–114)	–	
C-reactive protein (mg/L)	3.6 (3.2–187)	–	
Fibrinogen (mg/dL)	335 (183–696)	–	
Disease duration (years)	13 (1–37)	–	
Colchicine dose (mg/day)	1 (0.5–2)	–	

*Mann-Whitney U test. †Chi-square test. ‡T test. Data are shown as median (min–max), mean±SD and number, (%) as appropriate. P<0.05 was considered statistically significant. Atherogenic coefficient: Non-HDLc/HDLc; Atherogenic index of plasma: Log TG/HDLc; Castelli's risk index I: TC/HDLc; Castelli's risk index II: LDLc/HDLc; Non-HDLc: TC-HDLc. FMF: Familial Mediterranean Fever.

Table 2. Demographic and laboratory findings in male and female patients with Familial Mediterranean Fever

	FMF-Male (n=34)	FMF-Female (n=29)	p
Age (years)	29±6.3	28.6±8.2	0.890‡
Platelet ($10^3/\mu L$)	254 (150–343)	292 (158–627)	0.033*
Platelet distribution width (fL)	12.9±2	12.8±1.9	0.334‡
Mean platelet volume (fL)	10.6±0.8	10.7±0.8	0.992‡
Plateletcrit (%)	0.27 (0.16–0.40)	0.31 (0.19–0.62)	0.051*
Platelet large cell ratio (%)	30.5±6.5	30.8±6.4	0.838‡
Low-density lipoprotein cholesterol (mg/dL)	124.3±33.1	114.9±43.7	0.709‡
High-density lipoprotein cholesterol (mg/dL)	37.9±8.5	48.1±13.9	0.017‡
Total cholesterol (mg/dL)	192.1±46.5	184.4±48.2	0.368‡
Triglyceride (mg/dL)	109.2 (58.1–435.5)	98.1 (39.2–209.9)	0.144*
Non-HDLc	154.2±45.1	136.3±43.3	0.062‡
Castelli's risk index I	5.0 (2.8–11.5)	4.3 (2.7–6.1)	0.004*
Castelli's risk index II	3.3 (1.5–8.1)	2.2 (1.4–4.6)	0.007*
Atherogenic coefficient	4.0 (1.8–10.5)	3.3 (1.7–5.1)	0.004*
Atherogenic index of plasma	0.52±0.32	0.32±0.29	<0.001‡
Erythrocyte sedimentation rate (mm/h)	12 (2–114)	26 (6–83)	<0.001*
C-reactive protein (mg/L)	3.3 (3.2–187)	3.3 (3.3–144)	0.818*
Fibrinogen (mg/dL)	326 (183–631)	343 (274–696)	0.195*
Disease duration (years)	15 (1–32)	12 (3–37)	0.980*
Colchicine dose (mg/day)	1.5 (0.5–2)	1 (0.5–2)	0.195*

*Mann-Whitney U test. ‡T test. Data are shown as median (min–max) and mean±SD, as appropriate. P<0.05 was regarded as statistically significant. Atherogenic coefficient: non-HDLc /HDLc; Atherogenic index of plasma: log TG/HDLc; Castelli's risk index I: TC/HDLc; Castelli's risk index II: LDLc/HDLc; Non-HDLc: TC-HDLc.

the episodes of acute inflammation.[17] It has been suggested that the inflammation in FMF is related to endothelial dysfunction, platelet hyperactivation, and increased atherosclerotic burden.[5]

In our study, there was no significant difference in the platelet indices, which are thrombocyte activation indicators, between the FMF patients and the healthy controls. In parallel with our findings, Uluca et al. [18] did not find any significant difference in MPV and PDW levels between FMF patients and healthy controls. However, other researchers have found a significantly higher MPV level in FMF patients compared with healthy controls.[19,20] The discrepancy between these studies may arise from pre-analytical variables (sample collection procedure, whether or not the duration between sample collection and the analysis was standardized, etc.), and the methodological differences of analyzers.

Many studies have sought to determine the risk level for atherosclerotic and coronary artery disease using lipid profiles and lipid ratios. It has been demonstrated that calculated lipid ratios can be used as a stronger indicator than any other single lipid parameter in the prediction of the atherosclerosis progression.[21–23] There are very few studies investigating the role of any changes in the lipid profile and lipid ratios in accelerated atherosclerosis pathogenesis in FMF patients. Keles et al.[24] found a negative correlation between the TG/HDLc ratio and flow-mediated dilatation as an indicator of endothelial dysfunction in patients diagnosed with chronic inflammatory diseases, including ankylosing spondylitis and FMF. Icli et al.[25] detected a positive correlation between AIP values and carotid intima media thickness, which is used to define preclinical atherosclerosis, in FMF patients. In another study, it was found that AIP levels in FMF patients were significantly higher compared with healthy controls while HDL levels were lower.[26] Similarly, we found elevated AIP, AC, CRI-I and II results, and reduced

Table 3. Correlations of the atherogenic indices and lipid profile levels in Familial Mediterranean Fever patients with the other laboratory tests and disease duration

	LDLc (mg/dL)		HDLc (mg/dL)		TC (mg/dL)		TG (mg/dL)		Non-HDLc		CRI-I		CRI-II		AC		AIP	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Platelet (103/μL)	0.036	0.789	–0.010	0.942	0.050	0.708	–0.020	0.880	0.025	0.852	0.031	0.816	0.027	0.839	0.031	0.816	–0.012	0.930
PDW (fL)	0.012	0.933	–0.091	0.510	–0.057	0.678	–0.040	0.772	–0.042	0.762	0.082	0.554	0.088	0.525	0.082	0.554	0.090	0.512
MPV (fL)	0.129	0.347	–0.007	0.960	0.055	0.687	–0.062	0.652	0.051	0.709	0.056	0.682	0.117	0.394	0.056	0.682	–0.012	0.928
PCT (%)	0.077	0.575	0.013	0.924	0.082	0.548	–0.043	0.751	0.046	0.738	0.023	0.865	0.043	0.757	0.023	0.865	–0.043	0.752
P-LCR (%)	0.114	0.408	–0.006	0.966	0.030	0.826	–0.076	0.576	0.025	0.853	0.044	0.749	0.100	0.466	0.44	0.749	–0.012	0.931
ESR (mm/h)	–0.172	0.188	–0.087	0.507	–0.234	0.070	–0.171	0.188	–0.248	0.054	–0.184	0.156	–0.127	0.334	–0.184	0.156	–0.126	0.332
CRP (mg/L)	–0.201	0.123	–0.275	0.032*	–0.313	0.014*	–0.100	0.443	–0.250	0.052	–0.006	0.962	0.047	0.719	–0.006	0.962	0.035	0.790
Fibrinogen (mg/dL)	–0.089	0.524	–0.152	0.266	–0.126	0.360	–0.113	0.412	–0.103	0.454	0.001	0.995	0.045	0.749	0.001	0.995	–0.034	0.805
Disease duration (years)	–0.091	0.519	–0.269	0.049*	–0.150	0.278	0.093	0.506	–0.073	0.598	0.124	0.373	0.135	0.337	0.124	0.373	0.186	0.179

*p<0.05. AIP: Log TG/HDLc; AC: Non-HDLc/HDLc; CRI-I: TC/HDLc; CRI-II: LDLc/HDLc; Non-HDLc: TC-HDLc. AC: Atherogenic coefficient; AIP: Atherogenic index of plasma; CRI-I: Castelli's risk index I; CRI-II: Castelli's risk index II; HDLc: High-density lipoprotein cholesterol; LDLc: Low-density lipoprotein cholesterol; MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; P-LCR: Platelet large cell ratio; TC: Total cholesterol; TG: Triglyceride.

Figure 1. Scatter plot image of the correlation between CRP and HDLc in patients with FMF (n=61).

CRP: C-reactive protein; FMF: Familial Mediterranean Fever; HDLc: High-density lipoprotein cholesterol.

Figure 2. Scatter plot image of the correlation between CRP and total cholesterol in patients with FMF (n=61).

CRP: C-reactive protein; FMF: Familial Mediterranean Fever.

Figure 3. Scatter plot image of the correlation between disease duration and HDLc in patients with FMF (n=54).

FMF: Familial Mediterranean Fever; HDLc: High-density lipoprotein cholesterol.

HDL levels in FMF patients. These results demonstrate that AIP, AC, and CRI-I and II levels in FMF patients can be used as additional indices in the evaluation of atherosclerotic risk.

Several studies have reported that cholesterol levels were significantly lower in FMF patients receiving colchicine compared with those of healthy controls.[4,26,27] The low levels of lipids may be explained with the potential anti-atherogenic and lipid lowering effect of colchicine.[27–30] In contrast, Ugurlu et al.[31] demonstrated that the use of colchicine did not affect lipid levels in FMF patients. In the present study, a significant difference was not observed in terms of lipid profile parameters between the patients using less than or equal to 1 mg of colchicine and more than 1 mg. We also found no significant difference in cholesterol levels, with the exception of HDL cholesterol. A negative correlation was observed between the CRP and HDLc levels. Hence, based on the results of this study, we speculate that low HDL levels may be associated with the inflammatory process of FMF. These results demonstrate that the relationship between colchicine and lipid levels in FMF patients is contradictory. Further prospective studies on this issue are required.

Our results demonstrated that while in male FMF patients, the levels of AIP, AC, and CRI-I and II were higher compared with the female patients, the HDL levels were lower. In line with our findings, Icli et al.[25] reported that it is more likely to have high cardiac risk in male FMF patients. In another study, Davis et al.[32] stated that men had lower HDLc levels than women. This difference between men and women may arise from psychological, behavioral, and endocrine factors.[33,34]

The main limitation of this study is the small sample size and the retrospective design. We found that in FMF patients, while AIP, AC, and CRI-I and II levels were significantly higher than in healthy controls, HDL levels were lower. We suggest that increased AIP, AC, and CRI-I and II levels can be considered supplementary markers in the prediction of atherosclerotic cardiovascular disease in FMF patients, and particularly in male patients.

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