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Original Research Article

Atherogenic index as a predictor of atherosclerosis in subjects with familial Mediterranean fever

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ABSTRACT

Background and objective: Numerous inflammatory and innate immune pathways are involved in atherogenesis. We aimed to investigate the atherogenic index and other lipid parameters in individuals with familial Mediterranean fever (FMF), as a predictor of atherosclerosis.

Materials and methods: A total of 60 patients with FMF and 60 healthy age- and sex-matched controls were included in this study. The patients with acute infection, chronic metabolic and rheumatic diseases, use of drugs other than colchicine and smoking history were excluded. CRP, ESR, total cholesterol, triglycerides, LDL-C, and HDL-C levels of patients and the control group were measured. Atherogenic index (TG/HDL-C) was calculated.

Results: We found that the atherogenic index values of the patients were significantly higher than those of the control group. HDL-C levels were lower and ESR and TG levels were higher in patients. Total cholesterol, LDL-C and CRP levels did not differ significantly between the two groups. There was no significant difference in the values of total cholesterol, LDL-C, triglycerides (TG), HDL-C, and atherogenic indexes between the groups of patients with and without M694V mutation.

Conclusions: Elaboration of clinical models of inflammation-induced atherogenesis may further advance our knowledge of multiple inflammatory pathways implicated in atherogenesis

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and provide a useful tool for cardiovascular prevention. We believe that the atherogenic index also be used as a preliminary indication of accelerated atherosclerosis in FMF. However, large-scale prospective studies on this issue are needed.

1. Introduction

Familial Mediterranean fever (FMF) which is an autoinflammatory disorder characterized by brief recurrent attacks of pleuritis, peritonitis, arthritis and fever. FMF is an autosomal recessive hereditary disease [1]. The disease most commonly occurs in Jews, Turks, Armenians and Arabs. FMF takes place among the genetic causes of monogenic hereditary recurrent fevers (HRF) which exhibits monogenic genetic transition. The prevalence of FMF varies between 1/200 and 1/1000. Recent studies have shown that subclinical inflammation may continue in FMF cases, even in symptom-free periods [2]. Some investigators have observed more severe inflammation and disease in patients with a specific MEFV mutation [3–5].

Atherosclerosis is the main contributor to the global morbidity and mortality. It starts early in life, progresses slowly and asymptomatically with aging, eventually resulting in atherosclerotic cardiovascular disease, adverse vascular events and death. Staggering amount of evidence derived from clinical studies suggests that multiple immune and inflammatory agents orchestrate atherosclerotic vasculopathy throughout the whole course of atherogenesis [6,7]. Various algorithms for predicting coronary atherosclerosis have been established, most of which are based on large epidemiologic and cohort studies. Atherogenic index in recent years has started to gain importance as an indicator of atherosclerosis [8,9]. Cardiovascular (CV) diseases are a serious concern in chronic inflammatory diseases. Atherogenic index has been suggested to be less susceptible to disease activity variation during large periods of time. This makes it more attractive to be used in CV risk prediction in this group of patients as compared with lipids concentrations. We aimed to investigate the atherogenic index and other lipid parameters in individuals with FMF as a predictor of atherosclerosis.

2. Materials and methods

2.1. Patients and controls

The present study was conducted between August 2012 and October 2013 in the Departments of Internal Medicine and Medical Genetics, Faculty of Medicine, Afyon Kocatepe University Hospital. The study was conducted retrospectively using hospital records and included 68 patients diagnosed with FMF. The control group included 60 age- and sex-matched healthy subjects. Five FMF patients of whom all laboratory data were not obtained were excluded from the study. Patients and control group were recalled to the hospital, and those who agreed to be included in the study were questioned for any chronic disease, any risk factors, used drugs, age, sex, hyperlipidemia, smoking, dietary compliance and family history.

Exclusion criteria were as follows: the presence of any acute infection, coronary artery disease, peripheral artery disease, cerebrovascular diseases, pneumonia, diabetes mellitus, systemic hypertension, acute or chronic renal failure, nonalcoholic fatty liver disease, chronic liver disease, chronic obstructive pulmonary disease, obstructive sleep apnea, connective tissue disease, inflammatory bowel disease, allergic rhinitis, asthma and smoking history. Because of the presence of renal failure in three patients, we included 60 (91.2%) patients in this study. Our study was approved by the local ethics committee and conducted in accordance with the ethical principles described by the Declaration of Helsinki. Informed consent form was obtained from all participants before the study. The knowledge of the study participants were received from the recorded data of the patients' files.

2.2. Biochemical analysis

Laboratory data of biochemical analyses and inflammatory markers were obtained from hospital records of the patients when they were in symptom-free period. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), the total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels were measured and atherogenic index (TG/HDL-C) was calculated.

2.3. Mutation analysis

All data of genetic analyses of patients were obtained from hospital records in the Medical Genetic Department of our university hospital. All molecular examinations of patients who have FMF or possible FMF were performed in the laboratory of the Medical Genetics Department. Each patient had given 2 mL of blood sample in order to obtain genomic DNA; for this process, a Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN, USA) was used. Spectrophotometric analysis of DNA molecules (Nanodrop ND-1000) was done to detect the amount and purity of the molecule. The MEFV mutations (M694V, M694I, M680I and V726 located in the tenth exon, and E148Q located in the second exon) in patients were determined with the PCR-ELISA method using PRONTO FMF Kit (Pronto Diagnostics, Rehovot, Israel), while P369S, K695R, A744S, R202Q and R761H mutations were determined with an FV-PTH-MTHFR Strip Assay Kit (Vienna, Austria). The patients were divided into two groups according to the presence or absence of the M694V mutation to determine the relationship between genetic structure and atherogenic index, and two

groups were compared in terms of atherogenic index values. Also, the patients were divided into as-owner homozygous M694V mutation and no M694V mutation, and atherogenic index values were compared in order to verify the effect of the M694V mutation.

2.4. *Statistical analysis*

Continuous variables were presented as mean ± SD, and categorical variables were expressed as percentage. Kolmogorov–Smirnov test was used to evaluate the distribution of variables. The Student *t* test was used for continuous variables with normal distribution, and Mann–Whitney *U* test was used for continuous variables without normal distribution. A *P* value of <0.05 was accepted as the significant level. For statistical calculations, SPSS Statistical Software (SPSS for Windows, version 17.0; SPSS Inc. Chicago, IL, USA) was used.

3. Results

The mean age of the patients with FMF and the control group were 30.15 ± 6.67 and 28.67 ± 5.02 years, respectively. The ratio of men to women with FMF was 27:33, while it was 25:35 for the control group. The male/female ratio and mean age of the patients and the control group were both similar. All patients were given colchicine treatment, 3 times a day (3 × 0.5-mg tablets). Two groups were evaluated in terms of the CRP, ESR, TC, LDL-C, triglycerides (TG), HDL-C and atherogenic indexes. We found that the atherogenic index values of the patients were significantly higher than those of the control group ($P = 0.005$). Moreover, ESR and TG levels were significantly higher in the patients with FMF ($P = 0.03$ and $P = 0.003$, respectively). HDL-C levels were significantly lower ($P = 0.01$). The CRP, TC, and LDL-C levels did not differ significantly between the two groups. All the characteristics and the laboratory data of the groups were outlined in Table 1.

Table 1 – All the characteristics and the laboratory data of the groups.

Variables	FMF group ($n = 60$)	Control group ($n = 60$)	*P* value
Age, years	30.15 ± 6.67	28.67 ± 5.02	0.415
Female, *n* (%)	33 (55)	35 (58)	0.565
CRP, mg/dL	0.94 ± 0.71	0.45 ± 0.36	0.07
ESR, mm/h	14.1 ± 9.3	6.8 ± 6.5	0.03
TC, mg/dL	162.72 ± 44.56	156.13 ± 22.14	0.889
LDL-C, mg/dL	97.24 ± 31.62	93.34 ± 18.12	0.698
TG, mg/dL	117.64 ± 59.55	81.82 ± 14.25	0.003
HDL-C, mg/dL	43.69 ± 14.97	46.14 ± 8.15	0.01
Atherogenic index	3.15 ± 2.38	1.86 ± 0.43	0.005

Student's t test and Mann–Whitney U test was used. *p* value <0.05 was accepted as the significant level.
CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol, Atherogenic index: (TG / HDL-C).

When the patients were evaluated in terms of genetic mutations, there was no significant difference in the values of CRP, ESR, TC, TG, LDL-C, HDL-C, and atherogenic indexes between the groups of patients with and without M694V mutation. Genetic analyses of the cases were evaluated. Seven of the cases had homozygous M694V mutations. While the number of patients with M694V mutation as homozygous, heterozygous, or compound heterozygous was 37 (61.6%), the number of patients with the other mutations was 23 (38.3%). The results of genetic analysis of patients were shown in Table 2.

4. Discussion

In the past decade, it has became evident that upregulation of inflammation and autoimmune attack in apparent systemic disease such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) may highly accelerate atherogenesis and increase the risk of vascular events [10,11]. Clinical research studies in this field have led to the emergence of a new discipline, vascular rheumatology, which aims to clarify pathophysiology of rheumatic diseases and co-morbidities and to propose recommendations for primary and secondary prevention of vascular events in the general population. Clinical models of inflammation-induced atherosclerosis elaborated over the past decade are mainly based on the cardiovascular phenomenon described within the frames of high-grade inflammatory conditions. Much less attention has been paid to atherogenesis in low-grade inflammatory conditions, such as ankylosing spondylitis and FMF [12,13]. Though vasculopathic cellular and molecular agents are not fully explored within the frames of FMF, some inflammatory cytokines are believed to be the main inflammatory cells implicated in

Table 2 – Mutation types in FMF patients.

Mutations	Mutation type	No. (%)
No mutation	–	3 (5)
Homozygous	M694V	7 (11.6)
	M680I	2 (3.3)
	E148Q	1 (1.6)
	R202Q with M694V heterozygous	1 (1.6)
Heterozygous	M694V	7 (11.6)
	E148Q	7 (11.6)
	V726A	5 (8.3)
	A744S	1 (1.6)
	M680I	1 (1.6)
	K695R	1 (1.6)
Compound heterozygous	M694V/E148Q	5 (8.3)
	M694V/R761H	4 (6.6)
	M694V/M680I	4 (6.6)
	M694V/V726A	4 (6.6)
	M694V/M694I	4 (6.6)
	E148Q/P369S	2 (3.3)
	M694V/R202Q	1 (1.6)

endothelial dysfunction, oxidative stress and overproduction of adhesion molecules in this disorder [14,15]. In addition to the classical risk factors associated with the development of the atherosclerotic coronary heart disease in recent years, it has been studied a very new biochemical parameters such as triglycerides and plasma concentrations of triglyceride rich lipoproteins, lipoprotein particles size, apolipoprotein B, lipoprotein, homocysteine, CRP, adhesion molecules and growth factors like as predictors of the disease [16–20]. In a study by Naito, lipid levels, lipoproteins and some of their combined ratios of patients who underwent coronary angiography were investigated for 10 years. And was reported that, lipoproteins and some of their increased combined ratios (such as TG/HDL-C, LDL-C/TG, LDL-C/HDL-C) have a better statistical link with severity and prevalence of the coronary artery disease, instead of lipid levels [21]. In the pathogenesis of accelerated atherosclerosis in FMF patients, regarding the role of changes in lipid profile have not been studied sufficiently in the literature. To solve this deficiency, we have planned this work. In this study, in addition to changes in lipid profile in patients with FMF, we examined the levels of atherogenic index (increasingly important in atherosclerosis). We found that the atherogenic index values of the patients were significantly higher than those of the control group. HDL-C levels were lower and TG levels were higher in patients. TC, and LDL-C levels did not differ significantly between the two groups. These findings were in parallel with Naito's report. But different results are also available in the literature. In a study evaluating the laboratory findings of twins with FMF, LDL levels were higher [22].

When the patients were evaluated in terms of genetic mutations, there was no significant difference in the values of TC, LDL-C, TG, HDL-C and atherogenic index between the groups of patients with and without M694V mutation. About this subject, there are two studies in the literature and which have different results [23,24].

Our study is important as it is the first study in this area. As a result, we believe that in the pathogenesis of accelerated atherosclerosis in the patients with FMF of the role of changes in lipid profile should be investigated. This issue is certain that future large-scale prospective studies are needed.

5. Conclusions

Elaboration of clinical models of inflammation-induced atherogenesis may further advance our knowledge of multiple inflammatory pathways implicated in atherogenesis and provide a useful tool for cardiovascular prevention. We believe that the atherogenic index also be used as a preliminary indication of accelerated atherosclerosis in FMF. However, large-scale prospective studies on this issue are needed.

Conflict of interest

The authors state no conflict of interest.

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