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ORIGINAL PAPER

Evaluation of intima media thickness of the common and internal carotid arteries with inflammatory markers in familial Mediterranean fever as possible predictors for atherosclerosis

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Abstract The aim of the present study was to determine whether intima-media thickness (IMT) of the common (CCA) and internal carotid arteries (ICA) was increased due to chronic inflammation occurring in familial Mediterranean fever (FMF) patients compared to healthy controls. Erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), serum amyloid A protein (SAA), lipid profile and homocysteine levels were examined in 70 FMF patients [median age 14 years (range 4–24)] in an attack free period and in 50 healthy controls [median age 14 years (range 4–18)]. All the patients were homozygous or compound heterozygous for MEFV mutations. IMT of both CCA and ICA was evaluated with a high resolution B-mode ultrasonography. ESR, CRP, fibrinogen and SAA levels were significantly higher in FMF patients as compared to healthy controls ($P < 0.05$). Intima media thickness of the common carotid artery was found to be significantly higher in FMF patients when compared to those in healthy controls [0.37 mm (0.26–0.61) vs. 0.28 mm (0.21–0.35), $P < 0.001$]. The median ICA-IMT was significantly increased in the patients when compared to those in the controls [0.25 mm (0.18–0.44) vs. 0.22 mm (0.10–0.26), $P < 0.001$]. A positive correlation between CCA-IMT and SAA levels ($r = 0.24$, $P = 0.04$) was found while ICA-IMT positively correlated with ESR ($r = 0.31$, $P = 0.008$) and fibrinogen levels ($r = 0.30$, $P = 0.012$). Intima media thickness, an early predictor of atherosclerosis, may be associated with subclinical inflammation in children with FMF. Further studies will enlighten whether these patients will be predisposed more to coronary artery disease.

Keywords Atherosclerosis · Familial Mediterranean fever · Inflammation · Intima media thickness · Serum amyloid A

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever accompanied by abdominal, chest or joint pain, myalgia and erysipelas-like skin lesions [1, 2].

The MEFV gene encodes a protein of 781 amino acids termed pyrin or marenostrin, which is mainly expressed in mature granulocytes. Mutations in the MEFV gene are thought to lead to uncontrolled neutrophil activation and inflammation [3, 4]. Although FMF is a periodic disease, recent data have shown that subclinical inflammation is also present [5, 6]. The long term effects of subclinical inflammation in FMF are not well evaluated.

High resolution B-mode ultrasound measurement of the carotid artery intima media thickness (IMT) is a widely used feasible, reliable, valid, cost-effective and non-invasive method to assess atherosclerosis in research [7]. The carotid artery IMT validity is firmly supported by histologic studies that demonstrate a close correlation between carotid and coronary atherosclerosis and by ultrasonographic

measurements that correlate highly with histologic measurements of carotid artery IMT [8].

The aim of this study was: (1) to determine whether arterial wall thickening is advanced in FMF patients compared to healthy controls by measuring the intima media thickness of the common and internal carotid arteries and (2) to define clinical and laboratory features that could have impact on intima media thickness of carotid arteries in FMF patients.

Patients and methods

Patients

This study was approved by local ethical committee of Hacettepe University Faculty of Medicine. Informed consent/assent of the parents and/or the subjects was obtained. A total of 70 FMF patients without cardiovascular disease and amyloidosis, who have been followed-up at least for 3 years in Hacettepe University Faculty of Medicine Department of Pediatric Nephrology and Rheumatology were enrolled in the study. All of them had an attack-free period of at least 3 months. Age, sex and body mass index (BMI) matched 50 healthy children served as controls. The diagnosis of FMF was made according to the Tel Hashomer criteria [9] and was further confirmed by mutational analysis. The clinical data including age, gender, history of the disease, age at onset, age at diagnosis, presence of fever, abdominal pain, pleurisy, joint pain and frequency of attacks were obtained. Demographic and clinical information was recorded on the day of carotid IMT measurement. Body weight (kg) and height (m) were determined, and body mass index (BMI; kg/m^2) was calculated.

All the patients were receiving colchicine at a dosage of 1–1.5 mg/day depending on body weight.

Blood pressure measurements were based on three independent readings using a digital blood pressure monitor after the subjects rested in the seated position at least 10 min. The subjects' right arm was used to obtain blood pressure measurements. The cuff size selected was based on the fourth report on diagnosis, evaluation and treatment of high blood pressure in children and adolescents [10]. *Z* scores for both systolic and diastolic blood pressures of each patient were calculated as described elsewhere [10]. On the day of carotid IMT measurement after an overnight fast, blood samples for erythrocyte sedimentation rate, C-reactive protein, fibrinogen, serum cholesterol, triglycerides, high density lipoprotein (HDL) and low density lipoprotein (LDL) and homocysteine levels, which had been determined by standard methods, were drawn from each subject.

Serum amyloid A (SAA) levels were measured by a solid phase sandwich ELISA method (Biosource International Cytoscreen, Human SAA Immunoassay Kit).

Mutational analysis for MEFV gene

Mutational analysis was performed in all the 70 patients. Our procedure for mutational analysis consists of two steps. The hot spot exon 10, which harbors 14 mutations, is first analyzed by denaturing gradient gel electrophoresis (DGGE). According to the band pattern, subsequent analysis is carried out either by restriction endonuclease enzyme digestion or sequencing. Furthermore, E148Q in exon 2 is analyzed by restriction endonuclease enzyme digestion.

Intima media thickness measurement

The carotid arteries were evaluated in all the patients and control subjects, with a high resolution B-mode ultrasonography (Antares, Erlangen, Siemens) using a 13.5 MHz multi-D linear transducer in multiple projections to optimize detection of carotid IMT. The ultrasonographic examination was performed by an experienced radiologist, who was blinded to the study groups. The ultrasonographic scanning was performed with the subject in the supine position, examining the CCA and ICA bilaterally in every subject. The carotid arteries were explored with longitudinal and transverse scans. The transducer was manipulated so that the near and far walls of the CCA and ICA became parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 10 mm proximal to the carotid bifurcation for CCA and a region 10 mm distal to the carotid bifurcation for ICA were identified, and the IMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The IMT measurement was obtained from both sites. The average of the four measurements for CCA and the average of the four measurements for ICA were used for analyses. All the measurements were made manually on still images obtained during the sonographic scanning.

The reproducibility of ultrasonographic measurements was calculated from repeated measurements of 20 subjects by 2 observers and was expressed by the repeatability coefficient: $RC = \sum Di^2/n$, where Di is the difference between each pair of measurements and n is the number of examined subjects [11]. The intraobserver and interobserver RC for carotid IMT were 4.2 and 2.2 μm, respectively, which were favorably comparable with previous studies [11, 12].

Statistical analysis

The results were analyzed using the SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and were expressed as

median (minimum–maximum) for data not showing normal distribution and as mean ± SD for data showing normal distribution. Parameters with non-normal distribution were compared using the Mann–Whitney *U* test. Correlation analysis was done by Spearman non-parametric correlation analysis. Variables that showed significant association in the univariate analysis were included in a stepwise multiple linear regression analysis to identify independent predictors of IMT. A value of $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics

The baseline characteristics of the study population are presented in Table 1. Whereas mean disease duration was 6.95 years, mean age of diagnosis was 5 years suggesting approximately 2 years delay between onset of symptoms and diagnosis. Initial presenting symptoms were as follows: fever (100%); abdominal pain (85%); arthritis/arthralgia (30%) and chest pain (10%). A total of 70% of the patients, who were under colchicine therapy had no attack in the last 12 months. While 20% of the patients had two attacks for a year, the remaining 10% had more than four attacks. Forty-five out of 70 patients (65%) were carrying homozygous M694V mutation. Of the 25 compound heterozygotes, 10 (15%) were carrying M694V/V726A; 10 (15%) were carrying M694V/M680I; 2 (3.5%) were carrying M694V/E148Q and 1 (1.5%) was carrying M680I/V726A.

Table 1 Clinical and laboratory characteristics of FMF patients and healthy controls

Variable	FMF patients ($n = 70$)	Controls ($n = 50$)	P*
Age (years)[a]	14 (4–24)	14 (4–18)	0.93
Sex F/M	30/40	24/26	ND
Height SDS	−0.72 ± 1.03	−0.24 ± 0.95	0.10
Body mass index (kg/m^2)[b]	21.91 ± 4.11	21.55 ± 2.63	0.32
Systolic BP (mmHg)	103.50 ± 11.17	104.40 ± 10.50	0.73
Systolic BP (*Z* score)	0.24 ± 0.86	0.23 ± 0.78	0.33
Diastolic BP (mmHg)	66.42 ± 6.97	66.73 ± 6.47	0.76
Diastolic BP (Z score)	0.37 ± 0.57	0.33 ± 0.29	0.35
Age at diagnosis (years)[b]	5.00 ± 4.03	–	
Disease duration (years)[b]	6.95 ± 3.02	–	
Treatment duration (years)[b]	5.75 ± 3.52	–	
ESR (mm/h)[b]	19.01 ± 3.8	7.96 ± 3.86	0.03*
CRP (mg/dl)[b]	0.79 ± 0.41	0.4 ± 0	0.02*
Fibrinogen (mg/dl)[b]	345.2 ± 45.5	284.2 ± 27.09	0.01*
SAA (μg/ml)	55.9 ± 51.6	14 ± 2.64	<0.001*
Cholesterol (mg/dl)[b]	123.2 ± 20.52	112.8 ± 16.7	0.431
Triglycerides (mg/dl)[b]	93.91 ± 25.26	89.07 ± 18.61	0.541
LDL-cholesterol (mg/dl)[b]	70.23 ± 14.4	67.5 ± 12.7	0.435
HDL-cholesterol (mg/dl)[b]	53.29 ± 17.9	43.4 ± 8.48	0.029*
Homocysteine (μmol/l)[b]	8.6 ± 1.5	8.28 ± 1.36	0.328

BP Blood pressure; *CRP* C-reactive protein; *ESR* erythrocyte sedimentation rate; *ND* not determined; *SAA* serum amyloid A

* *P* value <0.05 is significant

[a] Data are given as median (minimum–maximum)

[b] Data are given as mean ± SD

Laboratory parameters

Erythrocyte sedimentation rate, CRP ($N < 0.5$ mg/dl), fibrinogen (*N* 144–430 mg/dl) and SAA levels ($N < 20$ μg/ml) were significantly higher in FMF patients than in healthy controls (Table 1).

Intima media thickness of the common carotid artery was found to be significantly higher in FMF patients when compared to those in healthy controls [0.37 mm (0.26–0.61) vs. 0.28 mm (0.21–0.35), $P < 0.001$] (Fig. 1). Similarly, median value of intima media thickness of the internal carotid artery was significantly increased in the patients when compared to those in the controls [0.25 mm (0.18–0.44) vs. 0.22 mm (0.10–0.26), $P < 0.001$) (Fig. 2). Univariate correlation analysis was performed for both CCA and ICA-IMT and age at onset, disease duration, delaying in diagnosis, frequency of attacks, mutation type, systolic and diastolic blood pressures, serum lipid profile, acute phase reactants and homocysteine levels. A positive correlation between CCA-IMT and serum amyloid A levels ($r = 0.24$, $P = 0.04$) (Fig. 3) was found while ICA-IMT positively correlated with erythrocyte sedimentation rate ($r = 0.31$, $P = 0.008$) and fibrinogen levels ($r = 0.30$, $P = 0.012$) (Fig. 4). In multiple linear regression analysis, none of the parameters assessed could reach to statistically significance as an independent risk factor for intima media thickness of the common and internal carotid arteries in patients with FMF.

Discussion

Inflammation is considered as a major contributing factor for developing early atherosclerotic lesions. We and others have previously shown that a subclinical inflammation persists in FMF patients in between the attacks [5, 13]. In this context, this is the first study in children reflecting a clinical consequence of this inflammation since an early marker of atherosclerosis, namely IMT, was significant in patients with FMF. A few of papers in adults have studied IMT in FMF patients with some controversial results. Even from the same country, there are two conflicting reports where the

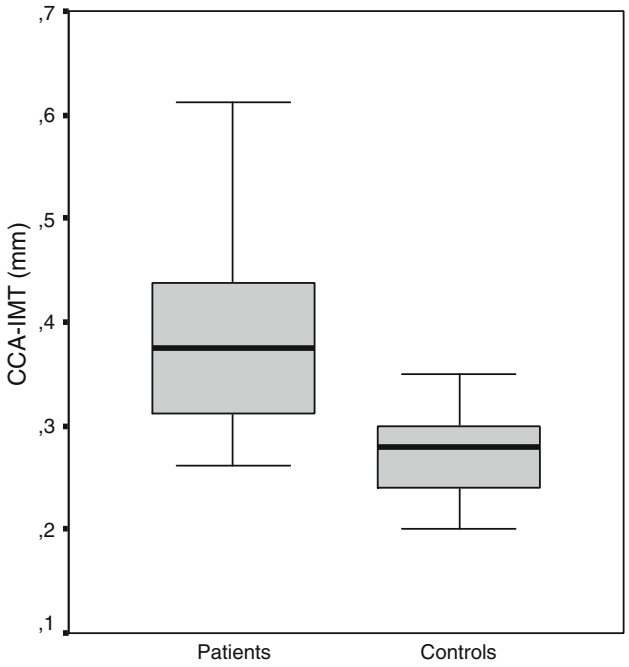

Fig. 1 Comparison of intima media thickness of the common carotid artery between patients with FMF and healthy controls

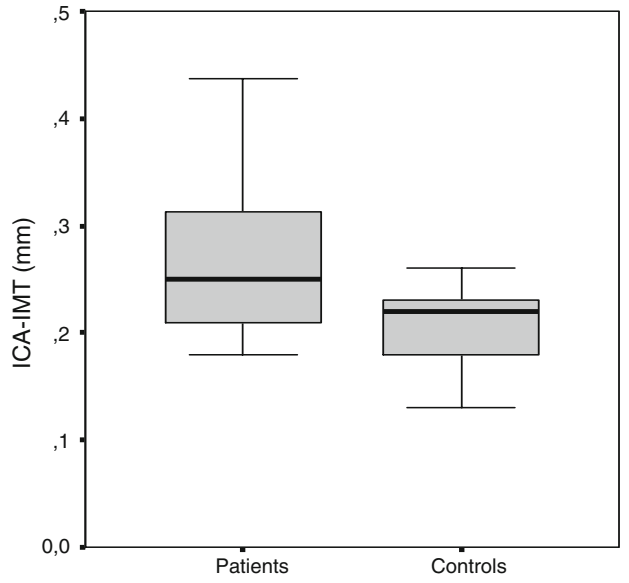

Fig. 2 Comparison of intima media thickness of the internal carotid artery between patients with FMF and healthy controls

one from central Turkey reports increased IMT (similar to our results) [14] whereas again a report from adult FMF patients from western Turkey shows no difference from healthy controls [15]. These differences may be due to confounding factors such as the compliance to colchicine, selection bias, dietary factors and maybe geographical factors.

Recent studies have suggested that inflammation is the major determinant of atherosclerosis [8]. The presented

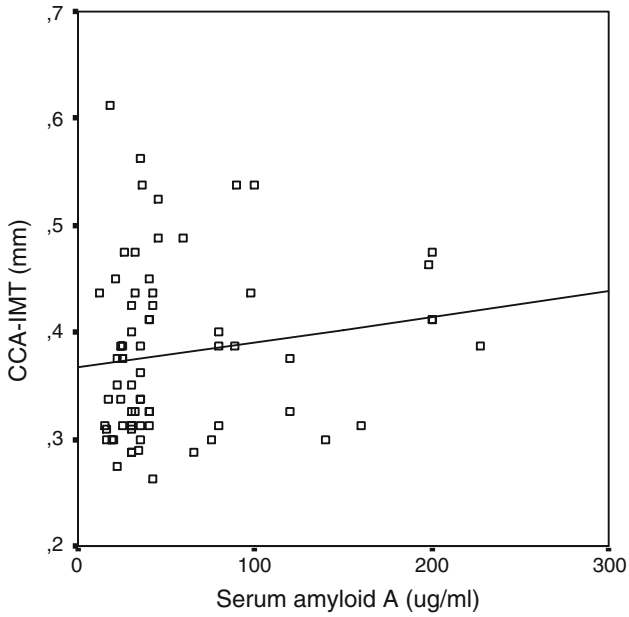

Fig. 3 Correlation of common carotid artery (CCA) with serum amyloid A level in patients with FMF

findings of this study not only support this concept but also highlight important implications of chronic inflammation in these children. Atherosclerosis can be considered to be a form of chronic inflammation that results from an interaction between modified lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall [7, 8]. It has been shown that substantial subclinical inflammation occurs widely and over prolonged periods in patients with FMF [5, 6]. In the present study, we found all markers of acute phase reaction (i.e. erythrocyte sedimentation rate, CRP, fibrinogen and particularly SAA) significantly higher in the patients even in attack free period when compared to those in the healthy controls. These findings were compatible with ongoing subclinical inflammation although there were no apparent clinical FMF attacks. We believe that the subclinical inflammation may explain the increased IMT in the patients. A recent study in an adult population from the same hospital, which has demonstrated that IMT of the carotid arteries was increased in FMF patients compared with healthy controls independent of known atherosclerotic risk factors further supports our observations [14]. The authors detected 2 atherosclerotic plaques out of 43 FMF patients despite increased IMT and attributed this result to their relatively young patient population [14].

In the present study, we found positive correlations between CCA-IMT and serum amyloid A (SAA) levels and between ICA-IMT and erythrocyte sedimentation rate and fibrinogen levels. Among the acute phase reactants, it has been shown that serum amyloid A (SAA) is the most sensitive one, which is produced in response to both acute and

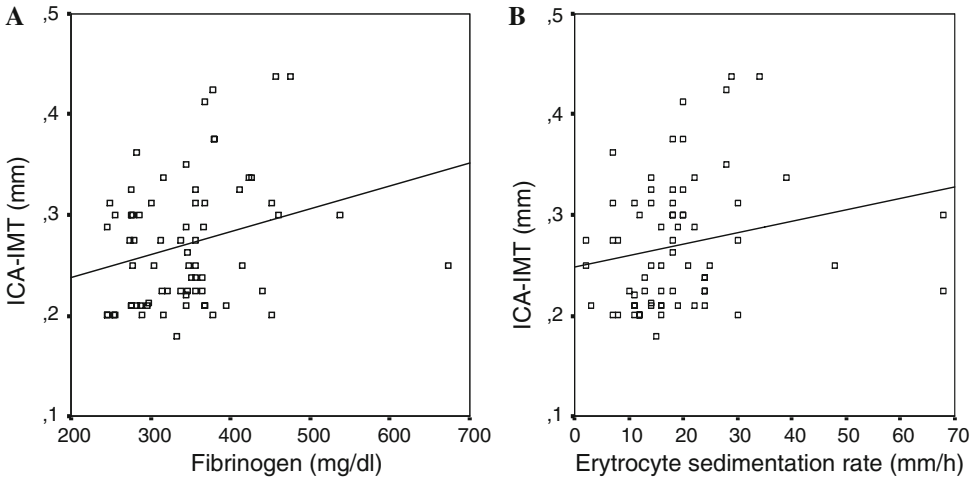

Fig. 4 Correlation of internal carotid artery intima media thickness (IMT) with erythrocyte sedimentation rate (**a**) and fibrinogen levels (**b**) in patients with FMF

chronic inflammatory stimuli, and whose levels may increase by as much as 1,000-fold [16]. We and others have clearly demonstrated that serum amyloid A (SAA) level proved to be the most sensitive marker of subclinical inflammation in FMF patients [5, 6, 13]. The major site of SAA synthesis, like that of most other acute phase proteins, is the liver and IL-1, TNF-alpha, and IL-6 are the principal cytokines involved induction of its synthesis in the liver. During an acute phase response or chronic inflammation, the capacity of the liver to degrade SAA also decreases, thereby contributing to the elevated circulating SAA levels observed under these conditions [17]. The function of this protein is elusive, but several lines of evidence suggest that they may have a role in atherosclerosis. First, SAA is found as an apolipoprotein on HDL particles and may play a role in acute modification of cholesterol transport during physiological stress [18]. In our study, higher HDL-cholesterol levels in the FMF patients might be related to this fact. Second, SAA has been shown to be chemotactic for monocytes [18]. Potential consequences include the stimulation of monocyte adhesion and chemotaxis into the arterial wall and increased delivery of cholesterol to cells of the arterial wall. These two processes might contribute to the initiation and progression of atherosclerotic lesions. Third, SAA is present in both mouse [19] and human atherosclerotic lesions [20]. SAA proteins can be produced by cells of the arterial wall [20]. In mouse models of hyperlipidemia it has been shown that SAA might be atherogenic because it adheres SAA-containing lipoproteins to vascular proteoglycans. Its ability to stimulate the expression of matrix-degrading enzymes, such as collegenases and matrix metalloproteinases could also contribute to plaque instability and plaque rupture [21]. Fourth, in genetic studies with mice, the induction of SAA expression associates with the development of fatty streak lesions in the aorta [22].

A chronic modest increase in SAA level appears to be associated with an increased risk of cardiovascular events. In a recent study, SAA and CRP levels were found to be independently associated with persistence of coronary lesions late after Kawasaki disease [23]. The authors suggested that inflammation might be a novel functional aspect of coronary artery diseases late after Kawasaki disease [23]. Despite widespread evidence that SAA is a moderate predictor of coronary heart disease, there are very few data published on the risk of heart disease in FMF [24, 25]. The only published paper by Langevitz et al. [26] suggests that colchicine-treated FMF patients have no increased cardiovascular risk compared to general population. In our study, we have shown that SAA correlated with the intima media thickness, which has proved to be an early predictor of atherosclerosis. The patients studied were receiving colchicine therapy and free of attacks for at least 3 months, so SAA levels were suppressed. This may explain why we found only a weak (but significant) correlation between its level and IMT. We speculate that if a patient remains untreated, SAA levels could show a more prominent correlation with IMT.

We and others have shown that the presence of MEFV mutations predispose to certain inflammatory diseases [27, 28]. Recently, Grimaldi et al. [29] have clearly demonstrated that after adjustment for well-recognized acute myocardial infarction (AMI) risk factors, the M694V allele predicted a significant risk to develop AMI in Sicilian population and have concluded that carrying proinflammatory M694 pyrin allele might increase AMI risk. In our FMF series, we found that M694V mutation was the leading one and was related to the most severe phenotype, including amyloidosis. Patients, who are carrying this mutation, frequently show subclinical inflammation even in attack free period when checked by SAA levels. This sub-clinical inflammation, if overlooked, may result in coronary artery disease and may explain findings of Grimaldi et al. [29].

In conclusion we have clearly demonstrated that intima media thickness, an early predictor of atherosclerosis, may

be associated with subclinical inflammation in children with FMF. Clinicians providing care for patients with FMF should be aware of this possible effect of chronic inflammation on vessels. We recommend monitoring of FMF patients for inflammation with SAA levels, not only erythrocyte sedimentation rate, CRP and fibrinogen levels, and adjusting colchicine dose accordingly. Suppression of the inflammation by adequate colchicine may prevent this complication as suggested. We also emphasize that these patients should be evaluated by intima media thickness to detect early arterio-structural changes for appropriate cardiovascular consultation. Larger longitudinal studies are still needed to clarify whether these patients have higher risk for hypertension, myocardial infarction or stroke than normal population.

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References

1. Bakkaloglu A (2003) Familial Mediterranean fever. Pediatr Nephrol 18(9):853–859
2. Ben-Chetrit E (2003) Familial Mediterranean fever (FMF) and renal AA amyloidosis—phenotype–genotype correlation, treatment and prognosis. J Nephrol 16(3):431–434
3. Stojanov S, Kastner DL (2005) Familial autoinflammatory diseases: genetics, pathogenesis and treatment. Curr Opin Rheumatol 17(5):586–599
4. Ozen S, Hoffman HM, Frenkel J, Kastner D (2006) Familial Mediterranean fever (FMF) and beyond: a new horizon. Ann Rheum Dis 65(7):961–964
5. Duzova A, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S, Ozaltin F et al (2003) Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheumatol 21(4):509–514
6. Tunca M, Kırkali G, Soytürk M, Akar S, Pepys MB, Hawkins PN (1999) Acute phase response an evaluation of familial Mediteranean fever. Lancet 353(9162):1415
7. Persson J, Forgren J, Israelsson B, Berglund G (1994) Ultrasound-determined intima-media thickness and atherosclerosis: direct and indirect validation. Arterioscler Thrombs 14(2):261–264
8. Schillinger M, Exner M, Mlekusch W, Sabeti S, Amighi J, Nikowitsch R et al (2005) Inflammation and carotid artery—risk for atherosclerosis study (ICARAS). Circulation 111(17):2203–2209
9. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T et al (1997) Criteria for the diagnosis of Familial Mediterranean fever. Arthritis Rheum 40(10):1879–1885
10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114(2 Suppl 4th Report):555–576
11. Aggoun Y, Sidi D, Levy BI, Lyonnet S, Kachaner J, Bonnet D (2000) Mechanical properties of the common carotid artery in Williams syndrome. Heart 84(3):290–293
12. Litwin M, Trelewicz J, Antoniewicz J, Wawer ZT, Wierzbicka A, Grenda R et al (2004) Intima media thickness and arterial elasticity in hypertensive children: controlled study. Pediatr Nephrol 19(7):767–774
13. Lachmann HJ, Sengul B, Yavuzsen TU, Booth DR, Booth SE, Bybee A et al (2006) Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 45(6):746–750
14. Akdogan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L et al (2006) Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 48(11):2351–2353
15. Sari I, Karaoglu O, Can G, Akar S, Gulcu A, Birlik M et al (2007) Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 26(9):1467–1473
16. Malle E, Steinmetz A, Raynes JG (1993) Serum amyloid A (SAA): an acute phase protein and apolipoprotein. Atherosclerosis 102(2):131–146
17. Uhlar CM, Whitehead AS (1999) Serum Amyloid A, the major vertebrate acute-phase reactant. Eur J Biochem 265(2):501–523
18. Badolato R, Wang JM, Murphy WJ, Lloyd AR, Michiel DF, Bausserman LL et al (1994) Serum amyloid A is a chemoattractant: induction of migration, adhesion, and tissue infiltration of monocytes and polymorphonuclear leukocytes. J Exp Med 180(1):203–209
19. Qiao J-H, Xie P-Z, Fishbein MC, Kreuzer J, Drake TA, Demer LL et al (1994) Pathology of atheromatous lesions in inbred and genetically engineered mice: genetic determination of arterial calcification. Arterioscler Thromb 14(9):1480–1497
20. Meek RL, Urieli-Shoval S, Benditt EP (1994) Expression of apolipoprotein serum amyloid A mRNA in human atherosclerotic lesions and cultured vascular cells: implications for serum amyloid A. Proc Natl Acad Sci USA 91(8):3186–3190
21. Chait A, Han YC, Oram JF, Heinecke JW (2005) Lipoprotein-associated inflammatory proteins: markers or mediators of cardiovascular disease? J Lipid Res 46(3):389–403
22. Liao F, Lusis AJ, Berliner JA, Fogelman AM, Kindy M, deBeer MC, deBeer FC (1994) Serum amyloid A protein family: differential induction by oxidized lipids in mouse strains. Arterioscler Thromb 14(9):1475–1479
23. Mitani Y, Sawada H, Hayakawa H, Aoki K, Ohashi H, Matsumura M et al (2005) Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: association between inflammation and late coronary sequelae in Kawasaki disease. Circulation 111(1):38–43
24. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A et al (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 350(14):1387–1397
25. Fyfe AL, Rothenberg LS, deBeer FC, Cantor RM, Rotter Jl, Luis AJ (1997) Association between serum amyloid A proteins and coronary artery disease: evidence from two distinct arteriosclerotic processes. Circulation 96(9):2914–2919
26. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolshy D et al (2001) Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J 3(1):9–12
27. Ozen S, Bakkaloglu A, Yilmaz E, Duzova A, Balci B, Topaloglu R et al (2003) Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation? J Rheumatol 30(9):2014–2018
28. Rabinovich E, Livneh A, Langevitz P, Brezniak N, Shinar E, Pras M et al (2005) Severe disease in rheumatoid arthritis patients carrying a mutation in the Mediterranean fever gene. Ann Rheum Dis 64(7):1009–1014
29. Grimaldi MP, Candore G, Vasto S, Caruso M, Caimi G, Hoffman E et al (2006) Role of the pyrin M694V (A2080G) allele in acute myocardial infarction and longevity: a study in the Sicillian population. J Leukoc Biol 79(3):611–615