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ORIGINAL ARTICLE

Arterial stiffness in Familial Mediterranean Fever: correlations with disease-related parameters and colchicine treatment

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Abstract

Introduction/objectives Familial Mediterranean Fever is the most common autoinflammatory disease. As chronic inflammation may result in increased arterial stiffness, we aimed to investigate indices of arterial stiffness in patients with Familial Mediterranean Fever and their associations with disease-related factors and colchicine treatment.

Method The study was conducted with 43 patients with Familial Mediterranean Fever, including 30 children, in attack free period and 42 healthy controls. Arterial stiffness was assessed by carotid-femoral pulse wave velocity and augmentation index.

Results Patients with Familial Mediterranean Fever presented similar carotid-femoral pulse wave velocity values to controls, but significantly higher augmentation index values (patients versus controls, 19.76% and 9.96%, $P < 0.05$). Augmentation index, adjusted for age and sex, was associated with complete response compared with partial response to treatment ($B = -17.78$, 95% CI −31.17 to −4.40, $P < 0.05$) and the presence of M694V.M680I genotype ($B = -16.75$, 95% CI −33.81 to 0.30, $P = 0.05$). Carotid-femoral pulse wave velocity presented an inverse relationship with colchicine treatment duration ($B = -0.003$, 95% CI −0.006 to −0.00, $P < 0.05$). Pulse wave velocity values adjusted for age and systolic blood pressure were associated with attack frequency ($B = 0.48$, 95% CI 0.01 to 0.96, $P < 0.05$). Addition of colchicine treatment duration to the model attenuated the association between carotid-femoral pulse wave velocity and attack frequency supporting the protective role of colchicine.

Conclusions The normal values of carotid-femoral pulse wave velocity in Familial Mediterranean Fever patients may reflect the compliance to colchicine treatment, which seems to have a protective role against arterial stiffness. However, the increased values of augmentation index need further investigation.

Key points

- *FMF patients are prone to present increased cardiovascular risk possibly due to inflammation.*
- *Colchicine treatment may have protective role against arterial stiffness in FMF.*
- *The normal values of cf-PWV in FMF patients may reflect the compliance to colchicine.*

Keywords Arterial stiffness · Augmentation index · Colchicine · Familial Mediterranean Fever · Pulse wave velocity

Introduction

Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease, affecting not only the populations arising from Eastern Mediterranean basin, but from different other ethnicities, even Japan [1]. FMF is characterized by recurrent, self-limited febrile attacks, typically accompanied by polyserositis along with elevated acute phase reactants, while arthritis, arthralgia, myalgia, and erysipelas-like erythema may also exist. The affected MEFV gene encodes the pyrin [2], a protein element of the NLRP3 inflammasome complex, which contributes to the exaggerated inflammatory response and excessive secretion of interleukin-1β (IL-1β) [3]. Importantly, it was observed that the severity of FMF disease is linked to the nature of the MEFV mutation and to the number of mutated alleles [4–6]. The p.M694V and M680I mutation are reported to have a relatively severe clinical course. Colchicine is the mainstay of treatment, and its daily use not only prevents FMF attacks, but also controls subclinical inflammation and protects from life-threatening

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amyloid A amyloidosis [7]. Inadequate response to colchicine in fully compliant FMF patients may be associated with genetic or environmental factors affecting disease activity [8].

Recurrent inflammatory process during the attacks, and the potential chronic persistent subclinical inflammation among attacks interval in FMF patients, may lead to endothelial dysfunction, attributed to arteriosclerosis. Accelerated atherosclerosis results in increased arterial stiffness, an independent risk factor of cardiovascular events and potential mortality in the general population but also in patients with inflammatory diseases [9]. Carotid-femoral pulse wave velocity (cf-PWV) is considered the gold standard for arterial stiffness evaluation as it has been estimated from its application to other chronic diseases [10, 11]. In the present study, we aimed to investigate indices of arterial stiffness, in patients with FMF and their associations with disease-related parameters and colchicine treatment.

Materials and methods

Study design

This is a single center, prospective, case-control study including young and adult patients with FMF, conducted in a pediatric rheumatology referral center from northern Greece. cf-PWV and aortic augmentation index (AIx75) was measured in the patient group, as well as in healthy controls and correlations with disease-related parameters and colchicine treatment were investigated.

Study population

A total of 85 individuals were consecutively enrolled in the study, 43 FMF patients attending the outpatient clinic for a six-monthly follow-up between September 2015 and June 2018, and 42 healthy volunteers. Adult patients (> 18 years) were included in the study, as they had been followed in the center until transition.

Inclusion criteria were as follows: (1) FMF patients, fulfilling the diagnostic Tel-Hashomer criteria; (2) age from two years old, including adults; (3) treatment with colchicine for at least six months. Exclusion criteria were as follows for both the patient and the control group: (1) known risk factors predisposing to atherosclerotic disease such as hypertension, hyperlipidemia, and diabetes mellitus; (2) other diseases including infection, neurological disorders, and chronic kidney disease and; (3) history of malignancy or any other conditions related to atherosclerotic risk.

The study complies with the 1964 Declaration of Helsinki and its later amendments and the institutional bioethics committee has approved the research protocol. Informed consent to participate in the study has been obtained from the parents or the participants themselves when age was greater than 18 years.

No precise information is available about the prevalence of FMF in Greece. Greeks are considered to be at "intermediate risk" [12]. Even if we suppose that the prevalence of the disease in Greece is 1/1000 and we would like to ensure that a 99% confidence interval of the prevalence is estimated with precision ± 2% (δ = 0.02 or 2%) then the sample size would be 17 patients. A sample size of 33 individuals in each group has been calculated to have 0.90 power with $a = 0.05$ to detect a mean difference of 0.9 m/s and SD 1.1 in PWV between groups (FMF patients vs. controls) based on previous data [13]. The present study recruited 43 FMF patients.

Patients' characteristics

According to the medical history, clinical and laboratory data from FMF patients were retrieved and analyzed, including demographic and anthropometric parameters, date of diagnosis, age at onset, age at diagnosis, lag time to diagnosis, family history, disease duration, genetic mutations, clinical phenotype, attacks duration and frequency, treatment duration, response to treatment (complete response, partial response, or no response), additional treatment, and disease outcome. Patients were further divided to subgroups according to full or partial response to treatment and frequency of disease attacks less or greater than two months. All our patients, apart from three, were receiving the standard treatment for FMF, which is colchicine. The initial dose was determined according to the age (≤ 0.5 mg/day for children < five years old, 0.5–1.0 mg/day for children five – ten years old, and 1.0–1.5 mg/day for children > ten years old and adults). If the response was not sufficient, then the colchicine dose was increased until remission was achieved. The final dose ranged between 0.5 and 3 mg per day. The reason that the three patients had not received treatment yet, was the delay of the parents to comply with treatment.

According to the recommendations published by European League Against Rheumatism (EULAR), partial response to treatment was defined as five or less attacks for at least six months in patients who had been receiving the maximum tolerated dose [14].

Study procedure

Participants in the study had provided an informed written consent for adults and parents and an assent when over eight years old. Baseline evaluation included medical history, physical examination, and laboratory tests for FMF patients. Laboratory results were obtained at the day of the examination or from the most recent visit and included white blood cell count (WCC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Branchial blood pressure (BP) was measured thrice in each participant in seated position with a cuff of the appropriate size and the mean of three measurements was used for the analysis.

cf-PWV and AIx75 were measured with the SphygmoCor XCEL device (software version 1.2, AtCor Medical, Australia), according to previous published guidelines [15]. The device has been previously validated for non-invasive measurement of cf-PWV and central systolic pressure (cSP) in both adults and children [16, 17]. cSP and AIx75 were derived from PWA analysis using oscillometry, with the participants in seated position, their back and arm supported during the measurement. Appropriate cuff size according to participant's arm circumference was selected among three different cuff sizes available by the manufacturer (small adult 17–25 cm, adult 23–33 cm, large adult 31–40 cm). The brachial cuff is initially inflated to measure patient's brachial systolic BP and diastolic BP. Five seconds later, the cuff is reinflated to a subdiastolic level of pressure to acquire a volumetric displacement signal and automatically captures the pulse wave analysis waveform for five s. Augmentation pressure was defined as the difference of aortic pressures between the second and first systolic peak. Augmentation index was calculated as the ratio of augmentation pressure to aortic pulse pressure and was expressed as percentage (%) and heart rate-adjusted AIx75 was estimated by the SphygmoCor software by adjusting AIx75 at an inverse rate of 4.8% for each ten beats per minute increase in heart rate [18, 19].

cf-PWV was calculated according to the equation PWV = $0.8 \times D(\mathrm{m})/t$ (s), where t denotes the transit time of the arterial pulse along the distance, and D the distance assimilated to the surface between the recording sites. Distance (d) for the XCEL device was measured as the linear distance from the carotid pulse palpation site to the top of the thigh cuff at centerline of the location of femoral artery. An algorithm, built into the SphygmoCor XCEL device, reduces the distance by an operator-measured distance from the site wherein the femoral pulse can be palpated to the top of the cuff. Transit time (t) was measured as the time between diastolic feet of the carotid and femoral pulse for both devices. Measurements were performed in supine position at the right carotid and femoral arteries. Two sequential recordings were obtained for each participant. Speaking and sleeping were avoided during measurements. cf-PWV in adults was compared with age-adjusted norms, according to published reference cf-PWV values [20]. Regarding the pediatric population, the cf-PWV values were evaluated and compared with sex-specific and height-specific reference tables [21]. cf-PWV was defined as cf-PWV greater than the 95th percentile for the age- or height-adjusted reference population. cf-PWV z score values, height and age adjusted in the pediatric patients, were also calculated.

Statistical analysis

The IBM SPSS 24.0 (SPSS Inc., Chicago, IL, USA) statistical package was used to analyze the data. Standard descriptive statistics, t test, or non-parametric methods (Mann-Whitney U test, x^2 test) were used as appropriate for the comparison between the groups. General linear model univariate analysis of covariance was used to examine the effect of disease-related factors and colchicine treatment duration on arterial stiffness indices after adjustment for possible covariates (age, systolic BP, clinical, and laboratory parameters). Estimated marginal means after Bonferroni adjustment for multiple comparisons were used to assess differences between the FMF subgroups after adjustment for covariates. P value < 0.05 was considered statistically significant.

Results

cf-PWV and AIx75 evaluation and correlations between patients and controls

The study included 43 patients with FMF and 42 healthy controls with similar age and sex distribution. Baseline

Table 1 Anthropometric and clinical data of patients and controls

	Patients ($n = 43$) mean ± SD/median (IQR)* or %	Controls ($n = 42$) mean ± SD/median (IQR)* or %
Age (years)	14.02 ± 9.37/12 (7–20)	13.33 ± 7.92/11 (7–17)
Sex	22/43 (51.2%)	21/42 (50%)
Height (cm)	143.12 ± 24.24	147.90 ± 21.44
Height z score	0.23 ± 1.06	0.61 ± 0.98
SBP (mmHg)	112.92 ± 11.31	114.96 ± 11.74
DBP (mmHg)	67.95 ± 8.84	71.52 ± 7.62
cSP (mmHg)	99.89 ± 10.35	100.82 ± 10.53
AIx75 (%)	19.76 ± 20.966/15.5 (7.66–31.00)	9.96 ± 17.99/9.8 ((− 1.41) − 18.00)
cf-PWV (m/s)	4.97 ± 1.05/4.31 (4.31–5.48)	5.04 ± 1.08/4.76 (4.2–5.96)

*In case of non-normal distribution

SBP, systolic blood pressure; *DBP*, diastolic blood pressure; *cSP*, central systolic pressure; *AIx75*, augmentation index; *cf-PWV*, carotid-femoral pulse wave velocity

demographic, anthropometric, clinical, and laboratory characteristics of the two groups are presented in Table 1. In the patient group, mean age was 14.02 ± 9.37 years with median duration of disease 89 months (IQR 42-178), while the mean age of healthy controls was 13.33 ± 7.92 years. Patients presented higher values of AIx75 compared with controls [19.76% versus (vs.) 9.96%, $P < 0.05$], but there were no statistically significant differences among patients and controls regarding systolic BP, cSP, and cf-PWV (Table 1). One FMF patient had cf-PWV > 95th percentile.

Evaluation of disease-related parameters in FMF patient subgroups

Among FMF patients, 93.02% were on colchicine treatment with median duration of treatment 80 months (IQR 18-166). Clinical and laboratory characteristics of the FMF patients are shown in Table 2. There were no differences in age, sex, systolic BP, and cSP among treatment response subgroups (full vs. partial response) or attack frequency subgroups (< two months vs. > two months). There were no differences in duration of disease and colchicine treatment, pathogenetic mutations' prevalence, WBC, ESR, and CRP among treatment response subgroups (full vs. partial response) or attack frequency subgroups (< two months vs. > two months).

Table 2 Clinical and laboratory data in FMF patients

Patients group	Median (IQR) or *n* (%)
WBC	7.37 (5.80–9)
ESR	12 (7–19)
CRP	0.4 (0.02–1.04)
Age at onset (years)	2.5 (1.16–5)
Age at diagnosis (years)	5 (3.08–7.83)
Colchicine treatment duration (months)	80 (18–166)
Disease duration (months)	89 (42–178)
Response to treatment groups	
Complete response	26 (60.5)
Partial response	14 (32.6)
No treatment	3 (6.9)
Attack frequency groups	
< 2 months	35 (81.4)
> 2 months	8 (18.6)
Genotype	
M694V.0	10 (23.25)
M694V.M694V	7 (16.27)
M680I.0	1 (2.32)
M680I.M680I	3 (6.97)
M694V.M680I	6 (13.95)
Other	16 (37.20)

Correlations of disease-related parameters with AIx75

There were also no differences in AIx75 according to the presence of pathogenetic mutations except for M694V.M680I genotype (33.71 ± 17.81% vs. 16.6 ± 20.53%, $P < 0.05$) (Fig. 1). AIx75 was also higher in those with partial response to treatment ($P < 0.05$) (Fig. 2). The differences in AIx75 between the two groups persisted even after adjustment for age and sex (estimated marginal means 14.25%, 95% CI 6.09 to 21.96 for full remission vs. 31.81%, 95% CI 21.40 to 42.58 for partial response, $P < 0.05$, Bonferroni adjustment for multiple comparisons). In univariate analysis of covariance, AIx75, adjusted for age and sex, was associated only with full remission compared with partial response to treatment ($B = -17.78$ 95% CI −31.17 to −4.40) $P < 0.05$), and the presence of M694V.M680I genotype ($B = -16.75$ 95% CI −33.81 to 0.30, $P = 0.05$), but not with colchicine treatment duration, disease duration, attack group frequency subgroup, WCC, ESR, or CRP.

Correlations of cf-PWV with disease-related parameters and treatment

There were no statistically significant differences in cf-PWV levels according to response to colchicine treatment (full vs. partial response), presence of pathogenetic mutations (mutation M694V.0 or M694V.M694V or M680I.0 or M680I.M680I yes/no).

There were also no differences in cf-PWV among attack frequency subgroups (< two months vs. > two months). However, after adjustment for age and SBP, the differences in cf-PWV between attack frequency became statistically significant (estimated marginal means 5.06 m/s, 95% CI 4.86–5.26 for attack frequency group < two months vs. 4.57 m/s, 95% CI 4.14–5.00 for > two months frequency group, $P < 0.05$, Bonferroni adjustment for multiple comparisons).

cf-PWV presented a positive association with age ($B = 0.09$, 95% CI 0.06 to 0.12, $P < 0.001$) and SBP ($B = 0.02$, 95% CI 0.01 to 0.04, $P < 0.005$) and a negative association with colchicine treatment duration $B = -0.003$, 95% CI −0.006 to 0.00, $P < 0.05$). A linear inverse relationship of cf-PWV with duration of colchicine treatment was evident even in the pediatric age range (3–18 years) (Fig. 3). In univariate analysis of covariance, the patients' group cf-PWV values adjusted for age and SBP associated with frequency of attacks (for < two months vs. > two months, $B = 0.48$ 95% CI 0.01 to 0.96, $P < 0.05$), but not with WCC, ESR, CRP, or disease duration. When duration of colchicine treatment was added to the model, the association between cf-PWV and frequency of attacks attenuated and became non-significant ($P = 0.059$).

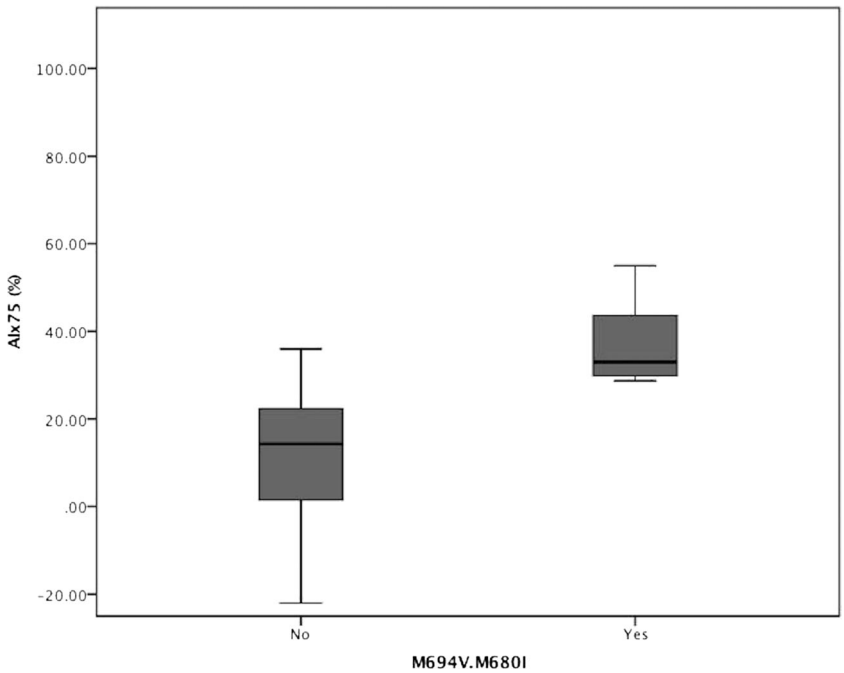

Fig. 1 AIx75 among FMF patients' subgroups: differences in FMF patients by the presence M694V.M680I genotype (yes vs. no)

Discussion

In the present study, we investigated indices of arterial stiffness in patients with FMF in order to assess early arterial alterations possibly due to chronic inflammation in this group of patients. Chronic inflammation has been related to both structural and functional arterial changes [22–24]. Endothelial dysfunction is associated with hypertrophy of smooth muscle cell and decrease in contents of extracellular matrix [25, 26]. An increase in circulating inflammatory mediators promotes white cell infiltration into arteries and the expression from smooth muscle cells of osteoblast markers that can take up phosphate to produce bioapatite, leading to medial calcification and reduced arterial distensibility [27]. Vessel infiltration and perivascular inflammation can lead to vessel ischemia, which may also promote matrix remodeling and eventually stiffening of the arteries. Previous studies have demonstrated that elevated arterial stiffness and wave

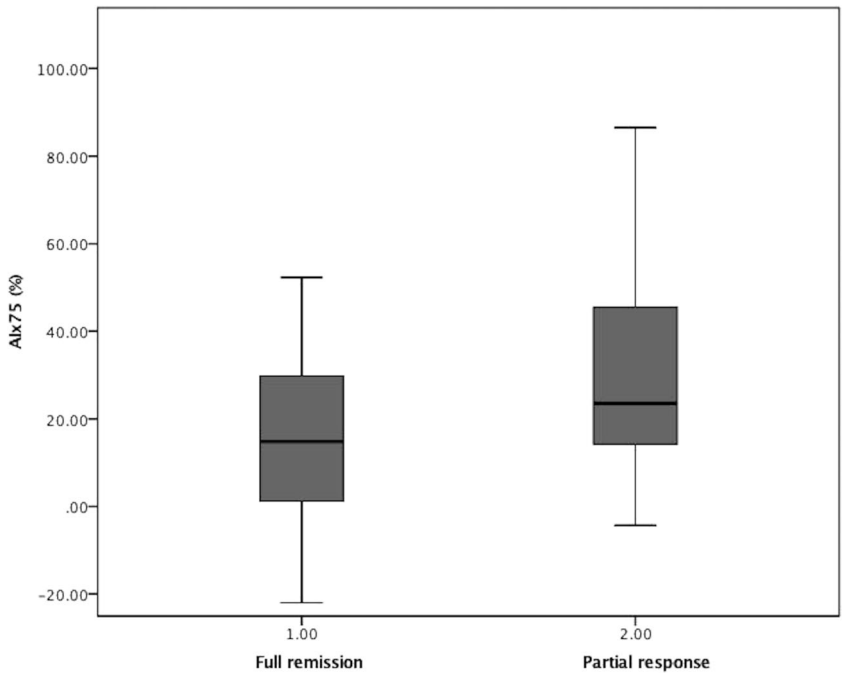

Fig. 2 AIx75 among FMF patients' subgroups: differences in FMF patients by response to colchicine treatment

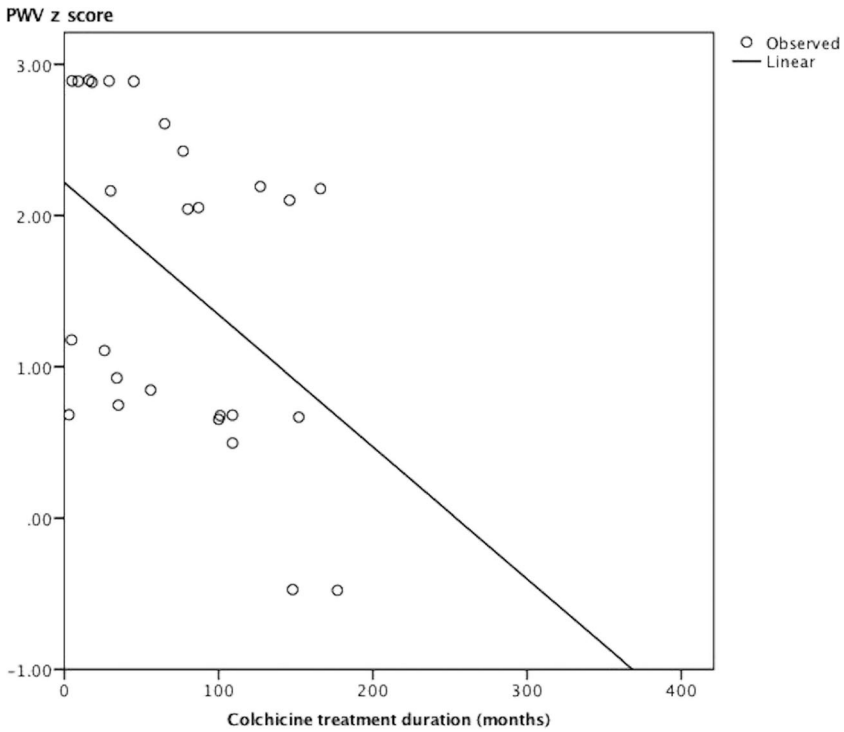

Fig. 3 Linear inverse relationship between cf-PWV *z* score values and colchicine treatment in the pediatric FMF patients

reflections are powerful and independent predictors of cardiovascular outcomes in different populations [28].

In FMF, patients experience inflammatory episodes that are characterized by elevation of acute-phase reactants (ESR, CRP, fibrinogen) and cytokines. However, it is not uncommon subclinical inflammation to exist even in symptom-free periods, making FMF patients prone to developing the life-threatening complication of FMF, AA amyloidosis [29, 30]. In the present study, cf-PWV measurements in FMF patients did not dissent from those of healthy controls, and in the majority of them (42/43), the values were normal, but we found an association of cf-PWV values with frequent attacks suggesting a potential negative impact of inflammation on arterial stiffness. However, arterial stiffness indices in our population did not correlated with common inflammatory markers including WCC, ESR, and CRP. There are few studies investigating arterial stiffness with the use of PWV in adult patients with FMF. Yildiz et al. demonstrated a slight increase in the cf-PWV in patients with FMF [31]. Two further studies by Yilmaz et al. (2014) and Cakar et al. (2017) also showed increased arterial stiffness in patients with FMF, but they included a significant proportion of patients during disease attacks [32].

The most interesting finding is that colchicine treatment duration was associated with lower cf-PWV values and attenuated the effect of disease attacks on cf-PWV, providing evidence for the cardiovascular protective role of colchicine in FMF. Kukuy et al. have also previously showed normal values of PWV in FMF and an association with colchicine treatment [33]. Of note, data on the prevalence of atherosclerotic cardiovascular disease in FMF patients are scarce [34]. Further studies need to be conducted in order to provide evidence for the cardiovascular risk of FMF patients and the beneficial effect of colchicine treatment.

In the present study, AIx75 was found to be increased among patients compared with controls. Response to colchicine treatment was an important predictor of AIx75 in the present study, implying that chronic inflammation could affect arterial stiffness. In a systematic review and meta-analysis, including 5648 participants, Vlachopoulos et al. showed that AIx75 constitutes a marker of atherosclerotic burden that provides a significant predictive value of cardiovascular events and mortality [35]. This discloses that AIx75 may comprise a sensitive marker of subclinical inflammation that leads to augmented arterial stiffness [36]. In addition, AIx75 was higher in FMF with M694V.M680I genotype, which is considered to be associated with severe disease phenotype. Thus, AIx75 needs to be further investigated.

The present study is not without limitations. Laboratory evaluation included only typical inflammatory markers. Moreover, the cross-sectional design of the study does not allow to establish causal relations between disease parameters and arterial stiffness. Finally, the study included a relatively small number of patients, but similar to previously published papers on the topic and according to sample size calculation adequate to detect differences among patients and controls. The small number of patients in the subgroups could have limited our ability to detect statistical associations. However,

we demonstrated statistically significant differences in PWV with a very good power of 0.99.

Our study has also several strengths. To our knowledge, this is the first study evaluating the arterial stiffness in FMF pediatric patients, supporting the beneficial effect of colchicine treatment in complete control of disease attacks, and minimizing subclinical inflammation among attacks.

In conclusion, the results of the present study may provide evidence for the increased cardiovascular risk in FMF patients possibly due to inflammation, as arterial stiffness indices were associated with response to colchicine treatment and duration of treatment. The normal values of cf-PWV in FMF patients may reflect the compliance to treatment with colchicine. Future studies need to assess longitudinally the beneficial effect of colchicine on cardiovascular risk in FMF patients.

Acknowledgments We thank the patients and their parents who participated in this study.

Compliance with ethical standards

Disclosures None.

Ethical standards The study complies with the 1964 Declaration of Helsinki and its later amendments and the institutional bioethics committee has approved the research protocol. Informed consent to participate in the study has been obtained prior to their inclusion in the study from the parents or the participants themselves when age was greater than 18 years.

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