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Original Article

Effect of amyloidosis and proteinuria on augmentation index in patients with familial mediterranean fever

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Abstract

Aim: Familial Mediterranean Fever (FMF) is an auto-inflammatory disease which is characterized by amyloid deposition in multiple organs.Pulse wave velocity (PWV) and augmentation index (AIx) are associated with cardiovascular diseases and important predictors of long term prognosis.We aimed to investigate effect of amyloidosis and amount of proteinuria on subclinical atherosclerosis determined by PWV and AIx in patients with FMF.

Material and Methods: Aortic pulse wave velocity (PWV), augmentation index (AIx) were measured in 35 FMF patients (12 amyloidosis and 23 non-amyloidosis) and in 34 control subjects.Demographic, clinical and laboratory features and aortic stiffness parameters were compared between three groups (control, FMF with and without amyloidosis).

Results: There was no difference between groups in terms of age, gender, and cardiovascular risk factors. AIx was higher in FMF patients with amyloidosis compared with FMF patients without amyloidosis and control group (respectively; p = 0.04, p = 0.006). AIx did not differ between FMF patients without amyloidosis and control group (p = 0.4).There was a positive correlation between AIx and amount of proteinuria in patients with FMF (r=0.51,p=0.002).Multivariable linear regression analysisdemonstrated that age, presence of amyloidosis and amount of proteinuria were independent factors affecting AIx.

Conclusion: AIx is increased in FMF related amyloidosis.Presence of amyloidosis and amount of proteinuria in patients of FMF may be associated with increased cardiovascular risk.

Keywords: Amyloidosis; aortic stiffness; atherosclerosis; familial mediterranean fever; nonamyloid kidney disease; proteinuria.

INTRODUCTION

Familial Mediterranean Fever (FMF) is an autoinflammatory, autosomal recessive disease which presents with recurrent febrile episodes. Involvement of serosal, synovial membranes and skin may occur during episodes. Self-limiting episodes usually last 1-3 days and acute phase reactants such as C-reactive protein (CRP), serum amyloid A (SAA) and erythrocyte sedimentation rate (ESR) usually increase during episodes (1). Increased incidence of anemia of chronic disease, decreased bone mineral density, splenomegaly, atherosclerosis demonstrate that disease activity is not solely limited to episodes (2, 3).A previous study demonstrated decreased endothelium-dependent flow-mediated dilation (FMD) and increased carotid intima media thickness (IMT), indicators of atherosclerotic process, were documented in patients of FMF (4). Increased inflammation and complex genotype-phenotype relationships may play role in atherogenesis in FMF (5).

Aortic stiffness parameters such as pulse wave velocity (PWV) and augmentation index (AIx) are recent measures of generalized atherosclerosis. Augmentation pressure (AP) is defined as the difference of early and late systolic peak pressures. AIx is the ratio of AP to pulse pressure (PP) and expressed as a percent (6). AIx is one of the most important measures used to assess arterial stiffness.

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Increased arterial stiffness results in increased AIx, which is an important predictor of long term cardiovascular prognosis (7). Previous studies showed that AIx can be used as an indicator of increased cardiovascular risk in several inflammatory and rheumatic diseases (8-10).

AA amyloidosis is the most important complication of FMF which causes nephrotic syndrome, progressive renal failure and end stage renal disease. Colchicine treatment was proved to be effective in prevention of FMF related amyloidosis.Impairment of FMD and increased asymmetric dimethyl arginine (ADMA) level, measures of endothelial dysfunction, have been showed in patients with FMF related amyloidosis (11).It has also been shown that proteinuria increases risk of cardiovascular event in both diabetic and non-diabetic patients (12).Amyloidosis is not the only cause of proteinuria in patients with FMF, non amyloid kidney disease (NAKD) is another cause of proteinuria.In our study, we aimed to investigate the effect of amyloidosis and amount of proteinuria on risk of atherosclerosis determined by PWV and AIx in patients with FMF.

MATERIAL and METHODS

Study Population

Thirty five patients with FMF and 34 control subjects similar in terms of age,gender and body mass index (BMI) were included in this cross sectional study. Patients were diagnosed according to the Tel-Hashomer criteria previously described (13). All patients with FMF were under colchicine treatment. Clinical, demographic and laboratory data of the subjects were recorded. Aortic stiffness was measured with SphygmoCor (AtCor Medical, Sydney, Australia) device. All examinations and measurements were performed during a 3 months of attack-free period which is evaluated with both clinically and biochemically (ESR, CRP). FMF patients were divided into two groups depending on presence of amyloidosis. Twelve patients with amyloidosis, diagnosed either by rectal or renal biopsy, and 23 non amyloidosis patients were compared. Biopsy was performed only in patients with high suspicion depending on clinical, laboratory (proteinuria, renal function tests) and renal ultrasound evaluation. NAKD was detected in renal biopsies of 5 patients with proteinuria. Two patients had IgA nephropathy, two patients had mesangial proliferative glomerulonephritis, and one patient had diffuse proliferative glomerulonephritis. Subjects with systemic diseases such as hypertension, coronary artery disease, diabetes mellitus,chronic obstructive pulmonary disease,acute infections, acute renal failure and subjects with a history of medication except for colchicine, angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) were excluded. There were no patients receiving TNF inhibitor, IL-6 receptor antibody or IL-1 inhibitor.Coronary artery disease excluded by coronary angiography in the last year or non-invasive stress tests in the last six months.All patients approved written informed consent and the study protocol was approved by ethics committee of Necmettin Erbakan University Meram Medicine Faculty in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

AIx andPWV Measurement

All participants were asked to avoid intake of caffeinated, alcoholic beverages and other stimulants within 3 hours and vigorous exercise within 24 hours prior to measurement. The participants had rest in supine position for 10 minutes before measurement at a room temperature of 20-23°C.PWV was measured by using SphygmoCor (AtCor Medical, Sydney, Australia) device. By this method, first carotid and then femoral pulse wave have been examined with simultaneous electrocardiography (ECG). Time elapsed between beginning of R wave and beginning of pulse wave was calculated automatically on ECG. Then the differences of time measured for femoral and carotid artery were calculated automatically by the device. This difference shows the time elapsed of propagation of the pulse wave from carotid artery to femoral artery. Thereafter the distance is measured on the body surface between the spots where the measurements for carotid and femoral arteries were performed. After this measurement, values were set on the device and aortic PWV was automatically calculated as m/s (Figure 1). AIx was measured noninvasively by SphygmoCor device. Pressure wave forms on radial artery was recorded by high-fidelity applanation tonometry (Millar Instruments, Houston, Texas). Central aortic wave form was automatically acquired by the SphygmoCor device. Pulse pressure and augmentation pressure were calculated on this wave form automatically. AIx was obtained by dividing augmentation pressure to pulse pressure. Since AIx is affected by heart rate, heart rate was normalized to 75 bpm (Figure 2). All measurements were performed by the same cardiologist, blind to the study and patients, who has experience with the device.

Statistical Analysis

Statistical analyses were applied using IBM SPSS Statistics for Windows, Version 19.0. (IBM Corp. Armonk, NY). Descriptive statistics are announced as mean ± standard deviation or median (25th-75th percentiles) values as appropriate. Normal distribution was evaluated using the Kolmogorov-Smirnov test. Chi-Square or Fisher's Exact test were used to compare categorical variables. One-way ANOVA with LSD post hoc analysis was used to compare continuous variables among groups, the Kruskal-Wallis test was used for nonparametric independent samples orwhen homogeneity of variance was not present. Mann-Whitney test for nonparametric independent samples for inter-group comparisons were performed to confirm significance. Correlations were evaluated by Pearson or Spearman's correlation tests, as appropriate. A multivariable linear regression analysis with enter model was performed to determinate the independent predictors of AIx.P values of less than 0.05 were accepted as significant.

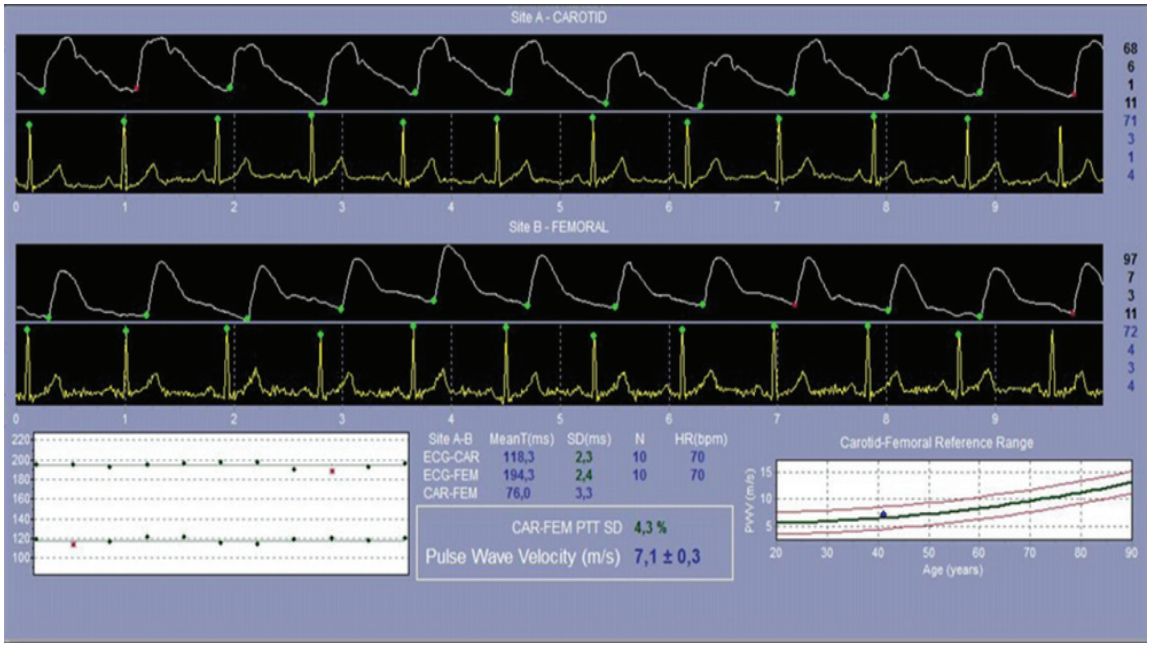

Figure 1. Samplemeasurement of Pulse Wave Velocity (PWV) by SphygmoCor device.Carotid pulse wave and femoral pulse wave were recorded with simultaneous ECG recording. PWV was calculated as m/sn and represented with a dot in a normogram (below right). Green lines show upper and lower 95th percentiles

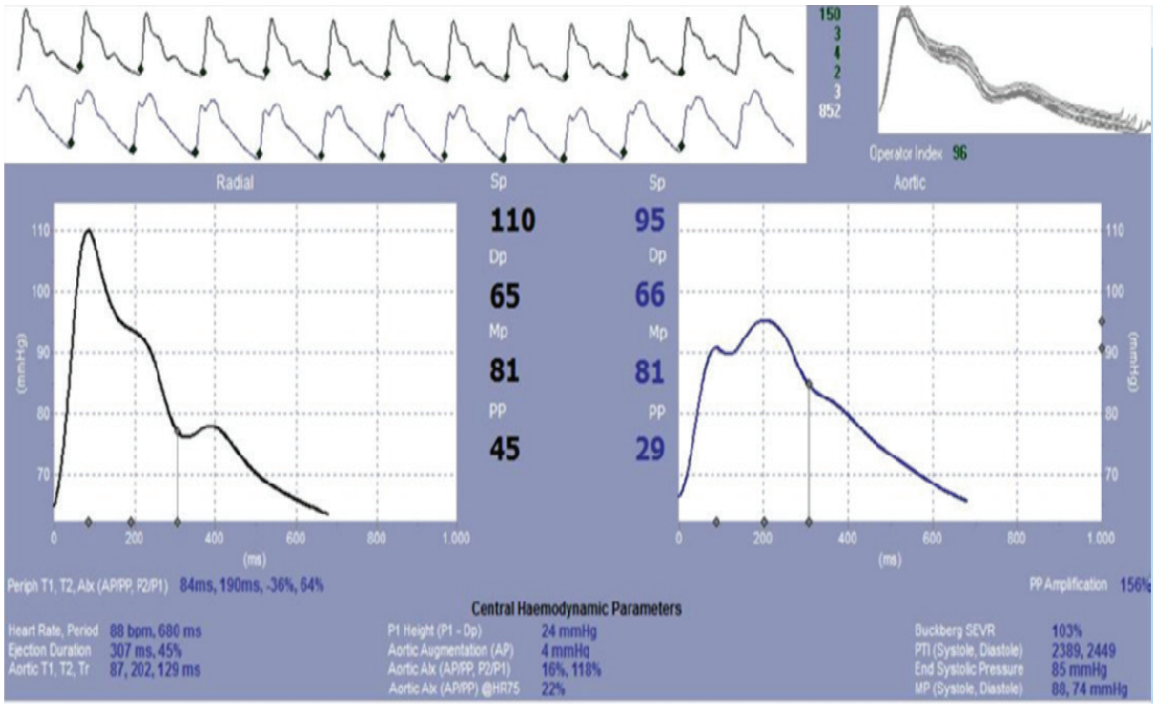

Figure 2. Sample measurement of Augmentation index (AIx) by SphygmoCor device. Radial pressures were recorded by applanation tonometry and central pressures were automatically generated. Figure 2. Sample measurement of Augmentation index (AIx) by SphygmoCor device. Radial pressures were recorded by applanation tonometry and central pressures were automatically generated

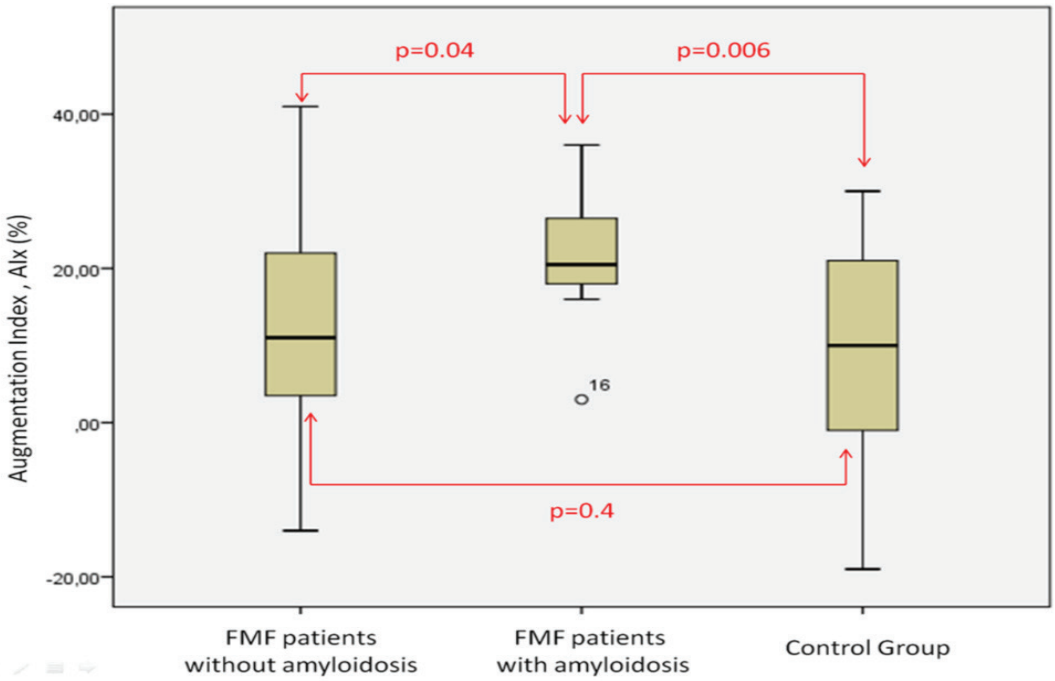

Figure 3. Augmentation index (AIx) measurements of three groups.

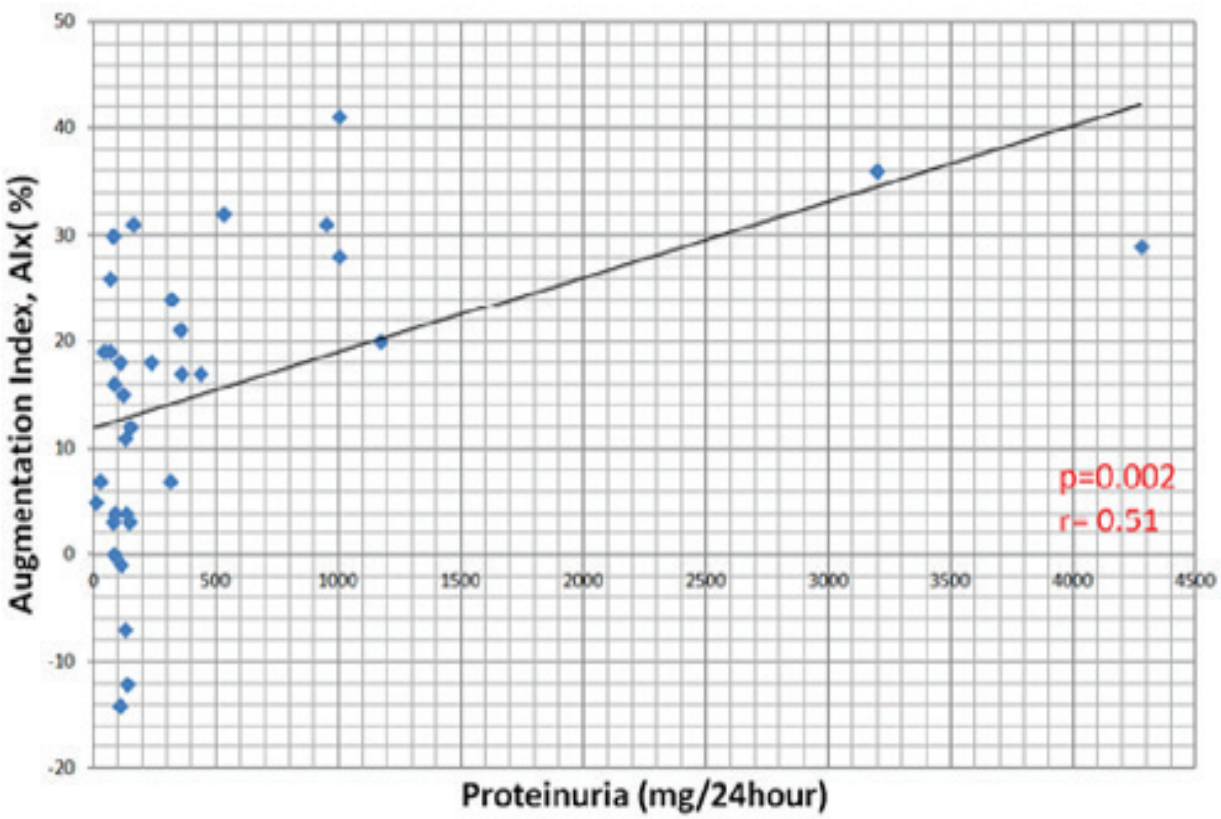

Figure 4. Correlation of Augmentation index (AIx) and amount of proteinuria in familial Mediterranean fever (FMF) patients

Table 1. The sociodemographic and laboratory parameters of three groups

	FMF patients with Amyloidosis (n=12)	FMF patients without Amyloidosis (n=23)	Controls (n=34)	P value
Age (years)	39.7 ± 8.0	39.0 ± 14.4	39.1 ± 12.5	0.98
BMI (kg/m2)	25.1 ± 2.4	25.5 ± 4.0	25.8 ± 4.5	0.88
Sex (male,%)	6 (50)	8 (34.8)	15 (44.1)	0.65
Smoking (n,%)	2 (16.7)	5 (21.7)	7 (20.6)	0.94
Creatinine (mg/dL)	1.05 ± 0.59	0.82 ± 0.15	0.83 ± 0.17	0.62
GFR(ml/min/1.73m²)	89.6 ± 36.9	96.8 ± 17.3	106.9 ± 33.6	0.18
Hb (g/dl)	13.2 ± 1.6	13.5 ± 1.6	13.4 ± 1.5	0.89
WBC (103/L)	7.58 ± 2.5	7.29 ± 1.7	7.0 ± 2.1	0.69
Plt (103/L)	233.7 ± 29.3	255.0 ± 59.1	244.3 ± 60.0	0.55
TC (mg/dL)	181.0(159.0-205.7)	163.0(150.0-202.0)	182.5(155.8-203.0)	0.87
TG (mg/dL)	116.0(88.0-138.5)	90.0(71.0-114.0)	90.5(71.8-116.3)	0.28
LDL (mg/dL)	104.9 ± 30.2	109.9± 39.5	108.8 ± 31.5	0.91
HDL (mg/dL)	51.4± 12.1	52.2 ± 13.1	51.8 ± 11.6	0.98
CRP (mg/dL)	4.0 (3.5-5.0)	3.5 (1.2-6.9)	3.2 (2.0-3.9)	0.17
ESR (mm/h)	10.0 (5.0-19.5)	9.0 (5.0-12.0)	9.0 (7.0-11.0)	0.75
Duration of colchicine therapy (years)	8.5±6.4	8.8±3.9		0.85
Delay from symptom onset to initiation of colchicine therapy (years)	8.4±4.2	7.0±5.7		0.44
Age at the beginning of FMF symptoms	22.8 ± 5.9	23.2± 8.7		0.88
Colchicine dosage (mg/day)	1.45±0.6	1.37±0.3		0.64
Proteinuria (mg/24 hour)	335 (80-1010)	130 (89-237)		0.16
Fibrinogen (mg/dL)	293.3±74.6	270.8±76.1		0.41
Ferritin (ng/mL)	68.1±46.2	47.0±34.6		0.14
CaxP (mg/dL)	32.9±3.3	34.0±5.5		0.53
Parathormone (pg/mL)	62.0±30.8	49.5±20.4		0.16
ACE inhibitors/ARB (n,%)	9 (75)	11 (47.8)		0.12
Duration of ACEi or ARB therapy (years)	7.6±4.9	6.3±4.1		0.23

FMF, familial Mediterranean fever; BMI, body mass index; GFR, glomerular filtration rate; TC, total cholesterol; TG, triglyceride; LDL, low density-lipoprotein cholesterol; HDL, high density-lipoprotein cholesterol; Hb, hemoglobin; WBC, white blood cell counts; Plt, Platelet; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CaxP, calcium-phosphorus product; ACE, angiotensin-converting enzyme; ARB,angiotensin receptor blocker

RESULTS

No difference was observed between FMF patients with and without amyloidosis and control group in terms of gender, age and BMI. Cardiovascular risk factors such as smoking and lipid parameters were not different between groups.Duration of colchicine treatment, colchicine dosage and, delay time from symptomonset to initiation of colchicine therapy were similar between FMF patients with and without amyloidosis.ACE inhibitor or ARB use to reduce proteinuria was not different between FMF patients with and without amyloidosis. There was no difference duration of ACE inhibitors or ARB therapy between FMF patients with and without amiloidosis. Baseline laboratory characteristics of groups involving proteinuria, estimated glomerular filtration rate (eGFR), hematologic and inflamatuar parameters were presented on Table 1. Central, peripheral blood pressure measurements and PWV were similar between groups. AP and AIx were significantly greater in FMF patients with amyloidosis compared with FMF patients without amyloidosis (p=0.018, p=0.04; respectively) and control group (p=0.002, p=0.006; respectively) (Table 2)(Figure 3). AP and AIx did

Table 2. Central, peripheral blood pressure measurements and aortic stiffness indices

	FMF patients with Amyloidosis (n=12)	FMF patients without Amyloidosis (n=23)	Controls (n=34)	P value
pSBP (mm Hg)	123.3 ± 12.2	123.4 ± 15.8	123.4 ± 15.8	0.54
pDP (mm Hg)	67.7± 9.9	66.5 ± 9.8	66.5 ± 9.8	0.94
pPP (mm Hg)	55.6 ± 9.2	56.9 ± 11.4	56.9 ± 11.4	0.30
cSBP (mm Hg)	111.3 ± 13.1	105.9 ± 13.9	105.9 ± 13.9	0.22
cDBP (mm Hg)	69.8 ± 10.9	67.6 ± 10.6	67.6 ± 10.6	0.82
cPP (mm Hg)	41.4 ± 7.6	38.3 ± 7.9	38.3 ± 7.9	0.05
MAP (mm Hg)	86.2 ± 10.4	85.3 ± 11.7	85.3 ± 11.7	0.87
AP (mm Hg)	9.9 ± 4.6	5.1 ± 6.1	5.1 ± 6.1	0.007
PWV (m/s)	9.5± 1.3	9.0 ± 1.3	9.0 ± 1.3	0.53
AIxHR75 (%)	24.4 ± 8.0	12.2 ± 13.6	12.2 ± 13.6	0.02
AIx (%)	21.7 ± 8.5	11.9 ± 14.6	11.9 ± 14.6	0.02

FMF, familial Mediterranean fever; pSBP, peripheral systolic blood pressure; pDP, peripheral diastolic blood pressure; pPP, peripheral pulse pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; MAP, mean arterial pressure; AP, augmentation pressure; PWV, pulse wave velocity; AIxHR75, augmentation index corrected for heart rate of 75; AIx, augmentation index

Table 3. Multivariable Lineer Regression Analysis to determine independent predictors of Augmentation Index

	B Unstandardized coefficients	Beta Standardized coefficients	p value
Constant	-34.442		0.118
Age	.922	.847	0.02
BMI	.188	.049	0.76
Proteinuria	.005	.324	0.04
Amyloidosis	7.578	.270	0.04
GFR	.095	.179	0.37
Delay Time of Colchicine Therapy	-.699	-.269	0.37

BMI, Body mass index; GFR, glomerular filtration rate

not differ between FMF patients without amyloidosis and control group.Mean AIx of 5 patients with NAKD was 24.8 ± 13.1 and was similar to those with amyloidosis. AIx of patients with NAKD was higher than control group and FMF patients without amyloid kidney disease (AKD) and NAKD (p=0.01, p=0.01 respectively).The Spearman's correlation test demonstrated that a positive correlation between AIx and amount of proteinuria in patients with FMF (r=0.51,p=0.002) (Figure 4). Multivariable linear regression analysis demonstrated that age, presence of amyloidosis and, amount of proteinuria were independent factors affecting AIx(p=0.02, p=0.04, p=0.04; respectively) (Table 3).

DISCUSSION

In this study, we have focused on the relationship between risk of atherosclerosis and amyloidosis in patients with FMF.Our findings showed that AIx is higher in patients with FMF related amyloidosis as compared to those without amyloidosis and control group. Additionally, significant correlation was found between AIx and amount of proteinuria in our study. We demonstrated that age, presence of amyloidosis and amount of proteinuria were independent predictors of greater AIx, which is an indicator of increased atherosclerosis, in patients with FMF.

Even at children, endothelial dysfunction due to increased inflammation was demonstrated in FMF (14). Several studies found increased carotid intima media thickness in patients with FMF. These studies raised suspicion of increased risk of atherosclerosis in FMF (15, 16). Moreover, another study demonstrated impaired coronary flow reserve in FMF patients (17). Impaired coronary microvascular dysfunction was attributed to endothelial dysfunction and early atherosclerosis.Latter studies showed increased PWV in FMF patients (18, 19). A recent study found similar PWV in FMF patients on colchicine treatment and healthy controls, this finding was attributed to cardiovascular protective effect of colchicine (20). However these studies neither particularly studied nor excluded patients with amyloidosis.

Most important complication which determines the prognosis in FMF is secondary amyloidosis. Renal amyloidosis and proteinuria are shown to be indicators of increased cardiovascular diseases and poor prognosis (21). Patients on peritoneal dialysis due to amyloidosis have the worst survival compared with other etiologies (22). FMF related amyloidosis was associated with increased mortality after renal transplantation when compared with non amyloidosis. Cardiovascular disease and infections were major causes of death in these patients (23). Yılmaz M et al. showed increased risk of cardiovascular mortality in FMF patients who develop nephrotic syndrome due to amyloidosis, but notend-stage renal disease (ESRD). They found increased levels of ADMA, CRP, pentraxin-3 in addition to low FMD in patients with FMF related amyloidosis compared with glomerulopathies and concluded that ADMA levels may be associated with increased mortality (13). Previous study showed impaired coronary flow reserve in patients with AA amyloidosis and concluded that patients with amyloidosis may have increased risk of coronary atherosclerosis (24). In our study, consistent with previous studies, we found elevated atherosclerosis risk as determined by AIx measurement in FMF related amyloidosis.

Another cause of proteinuria in patients of FMF is NAKD which is a heterogeneous group involving glomerulonephritis (such as mesangial IgA nephropathy, crescentic, rapidly progressing glomerulonephritis, diffuse proliferative glomerulonephritis, IgM nephropathy) and vasculitis (25, 26).It has been shown that NAKD patients have less proteinuria and less likely develop of ESRD compared with AKD in patients with FMF (25).Proteinuria is an increased risk for cardiovascular events in both diabetic and non-diabetic patients(12). Nevertheless, it is not clear whether increased risk of atherosclerosis due to NAKD related proteinuria in patients of FMF.However, in our study, we showed that, independent of amyloidosis, proteinuria increased AIx in patients with FMF. In addition, AIx of patients with NAKD were similar to those of AKD patients.These findings demonstrated that NAKD related proteinuria may increase atherosclerosis risk in patients with FMF.

AIx was found to be higher in patients with ESRD who underwent hemodialysis compared to healthy subjects (27). There were no patients with hemodialysis in our study group, and GFRs between groups were statistically similar. In addition, in multivariable linear regression analysis, it was shown that there were the effect of amyloidosis and amount of proteinuria on the augmentation index independent of GFR.

Since all FMF patients in our study were taking colchicine, AIx values of control group and FMF patients without amyloidosis were similar. This finding is compatible with previous studies which showed vascular protective effect of colchicine (28).In our study, increased AIx may indicate the association between amyloidosis and / or proteinuria and cardiovascular risk despite colchicine treatment in FMF patients with amyloidosis and/or proteinuria. Treatment of cardiovascular risks and investigation of presence of amiloidosis may be more careful in patients with increased AIx among FMF patients.

Limitations

Small amount of patients is the main limitation of our study. SAA level was unavailable which may provide furher information.The lack of biopsy from all patients may be a limitation of our study.

CONCLUSION

AIx is increased in FMF related amyloidosis. Presence of amyloidosis and amount of proteinuria in patients with FMF may be associated with increased cardiovascular risk. Nevertheless, larger studies are needed to investigate the relationship between cardiovascular risk and amyloidosis, amount of proteinuria.

Competing interests: The authors declare that they have no competing

interest.
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Ethical approval: The study protocol was approved by ethics committee of Necmettin Erbakan University Meram Medicine Faculty (2019/1850) in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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