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# Inflammation and cardiovascular disease in familial Mediterranean fever. An analysis of hospital admissions for acute cardiovascular event

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FMF-disease severity

## ABSTRACT

**Objective.** Patients, suffering from inflammatory disorders, are at an increased risk to develop cardiovascular disease (CVD). Here, we examine whether in familial Mediterranean fever (FMF), a model of inflammatory diseases, inflammation also increases the risk to develop cardiovascular (CV) disease.

**Methods.** To explore the role of inflammation in the occurrence of CVD in FMF, we identified all FMF patients  $\leq 55$  years old with CVD, admitted to our centre over a 15-year period. Correlates of inflammation, such as severity of FMF and dose of colchicine, as well as the presence of traditional CV risk factors were compared between the FMF patients with CVD (FMF-CVD) and control FMF patients without CVD.

**Results.** Twenty-three FMF-CVD and 40 control patients were compared. The severity of FMF, and the dose of colchicine, were similar in the 2 study groups; therefore, not associated with CVD. Compared with FMF patients without CVD, the FMF-CVD group comprised a higher proportion of men (78 vs. 40%  $p=0.005$ ), and of patients with diabetes (31 vs. 7%,  $p=0.016$ ) and inflammatory comorbidities such as Behçet's disease (30 vs. 7%,  $p=0.005$ ). Multivariate analysis revealed that only diabetes mellitus and inflammatory comorbidities were independent factors associated with FMF-CVD.

**Conclusion.** In FMF patients treated with colchicine, CVD is not associated with FMF-related inflammation.

## Introduction

Familial Mediterranean fever (FMF) is the prototype of autoinflammatory disorders (1). The disease is characterised by bouts of inflammatory serositis and chronic inflammation and is associated with mutations in pyrin, the product of

the Mediterranean fever gene (MEFV) (2). Colchicine prophylaxis usually suppresses the inflammatory bouts, but chronic inflammation may persist in about one-third of patients, particularly in those refractory to treatment (3). Chronic inflammation, with circulating inflammatory proteins and activated cells of the immune system, have been found to predispose to increased occurrence of atherosclerosis and cardiovascular disease (CVD) (4-12). Indeed, an increased risk for CVD by as much as twice the expected rate in the general population has been reported for rheumatoid arthritis (RA), psoriatic arthritis and other inflammatory disorders (13-17).

In contrast, despite being a model of inflammatory disorder, it is still unclear whether the inflammation of FMF forms a risk for the development of CVD. On the one hand, all 3 studies, which have evaluated the actual prevalence of CVD in FMF found it to be similar to that of the general population (18-20). However, on the other hand, the number of these studies is low and they have certain limitations; in one CVD was determined based solely on patient statement; and in the other two, the presence of cardiovascular (CV) morbidity was not the primary endpoint of the study.

Moreover, a series of studies, looking at subtle indices of CVD in patients with FMF, such as carotid intima-media thickness or the elasticity of blood vessels, yielded conflicting results. Some have identified increased prevalence of subclinical CVD (21-24), but others disagreed with these results (25-27). Thus, the evidence for an association between FMF and CVD is meager. More data on this issue are needed, and different strategies to discern the role of inflammation on the occurrence of CVD in FMF must be employed.

Competing interests: none declared.

## Materials and methods

### Study overview

The aim of the present study was to explore the possible association between the inflammation of FMF and CVD. The strategy employed here was to determine whether patients with FMF and CVD (FMF-CVD group) have more inflammation than their adjusted counterparts, who have FMF without CVD (FMF-control group). For that purpose, we compared the FMF and CV features of FMF patients admitted to the hospital for acute CV event, with those of randomly recruited FMF patients without CVD. We assumed that a higher severity score and a higher dose of colchicine in the FMF-CVD patients might reflect a higher burden of inflammation. We analysed the role of traditional risk factors as well. However, to reduce to a minimum their effect, we limited the age of the patients with and without CVD to  $\leq 55$  years. We performed the study in our tertiary medical centre serving a population larger than 500,000 individuals, a volume large enough to allow for the effect of inflammation of FMF on CV risk to be identified (data not shown). The local institutional review board approved the study (SMC-13-0906).

### Inclusion criteria

#### – FMF-CVD group

All FMF patients, aged 55 years or younger, admitted to our medical centre over a 15-year period (between January 2000 and December 2014) with an episode of acute CVD, were included in the analysis. The diagnosis of FMF was based on published criteria (28). The spectrum of CVD comprised a variety of diseases resulting from vascular ischaemia to the heart, brain or limbs (Table I). Patients admitted with at least one of the diagnoses detailed in Table I were identified using the computerised system of the medical centre. The institutional review board waived the need to sign an informed consent by patients of this group, conforming to the rules for studies based on data retrieved from patients' files

#### – FMF-control group

The control group consisted of con-

secutive patients (to avoid bias) who arrived at the FMF clinic for their annual/semiannual follow-up visits during January to March 2015. They had been diagnosed with FMF, according to published criteria (28), were aged 55-years old or younger and not affected by CVD, as delineated in Table I. All patients of the control group signed an informed consent, since contrary to the FMF-CVD patients they were recruited during their visit to the FMF clinic. However, data for the patients of this group was abstracted from patients file similarly to data obtained for patients of the FMF-CVD group. Thus, the mode of recruitment, used to improve random selection, did not affect the retrospective design of the study for this group.

### Exclusion criteria

Patients were excluded from the analysis if they did not conform to the inclusion criteria, refused or were unable to sign an informed consent (FMF-control group), lacked data confirming their FMF diagnosis, lacked data validating the occurrence of CV event (FMF-CVD group) or presented with data suggesting possible CVD (FMF-control group).

### Assessment

Patients' files were reviewed to abstract relevant data regarding their FMF characteristics and comorbidities. FMF specifications included: age at FMF onset, the sites involved in the FMF attacks during the course of the disease, the mean frequency of FMF attacks and their duration, and the current dose of colchicine. Based on these data, the severity score was determined, using the Mor scale (SS-2, designed for patients treated with colchicine) and defined as mild, intermediate or severe (29). In patients who have undergone genetic testing, the MEFV mutations were obtained as well.

Traditional CV risk factors were determined as present, if recorded in the patients' files. These factors included hypertension (blood pressure  $\geq 140/90$  mm Hg), hyperlipidemia (low-density cholesterol  $>100$  mg/dcl), smoking (current, past  $\geq 10$  pack years), diabe-

tes mellitus (haemoglobin A1C  $\geq 6\%$ ) and obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>). Treatment for any of these conditions determined its presence as well. The presence of additional inflammatory diseases such as RA, systemic lupus erythematosus, psoriatic arthritis, Crohn's disease, ankylosing spondylitis, was also determined, based on medical files.

In FMF patients with CVD, data were retrieved to further characterise the CVD, regarding its type, age of diagnosis and outcome. The diagnoses of the various forms of CVD were as given by the treating physicians. The main forms of CVD were cerebrovascular accident (CVA), or transient ischaemic attack (TIA), which in general were determined by the presence of neurological symptoms and signs, and computerised tomography of the brain. Renal artery stenosis was diagnosed based on angiography. Coronary heart disease was determined in all cases using coronary catheterisation. Based on the results of the angiography, the extent of coronary disease was roughly characterised by the degree of stenosis, number of vessels involved and length of the atheromatous lesion.

### Statistical analysis

Univariate analysis was performed using chi square or Student *t*-test, or by comparing proportions, as appropriate. Multivariate analysis was performed using logistic regression, which accounted for potential risk factors, as implied from the increased rate in the univariate analysis, and from the study assumptions (variables: diabetes mellitus, inflammatory comorbidities, male sex, colchicine dose, disease severity). A *p*-value  $<0.05$  was considered significant.

To determine the minimal sample size required to detect increased inflammation in the FMF-CVD group as compared to the FMF-control group, we used disease severity as a measure reflecting inflammation. We assumed that the fraction of patients with severe disease will be larger in the FMF-CVD group than in a random sample of FMF patients (FMF-control group), which is about 40%, while it is about 80% in the

**Table I.** Ischaemic cardiovascular diseases used to identify patients for the study group.

Disease classification according to the organ affected	Diagnosis
Ischaemic cardiac disease	Myocardial infarction Acute myocardial infarction ST-elevation myocardial infarction Acute coronary syndrome Ischaemic heart disease Unstable angina or angina pectoris Non ST-elevation myocardial infarction Ischaemic cardiomyopathy Congestive heart failure CHF exacerbation Left-sided heart failure Right-sided heart failure
Cerebro-vascular disease	Cerebrovascular accident Ischaemic stroke Transient ischaemic attack Transient cerebral ischaemia
Peripheral organ involvement with vascular ischaemia	Peripheral vascular disease Ischaemia/infarct (to any other organ such as the spleen, kidneys and intestine/bowel)

**Table II.** Characteristics of the single FMF patient with CVD but without CV risk factors.

Features	Details
Type of CVD	Acute myocardial infarction
Age at acute MI	49 years
Severity of FMF (by Mor score)*	Mild
Age of onset of FMF	10 years
Frequency of FMF attacks	Less than 1 per month
Number of sites involved during an attack	One
Number of sites involved along the disease course	2
Colchicine dose	2 mg per day
MEFV genotype	M694V/E148Q

CV: cardiovascular; CVD: cardiovascular disease; FMF: familial Mediterranean fever; MEFV: Mediterranean fever gene; MI: myocardial infarction.

\*Mor: FMF severity score (29).

**Table III.** CVD types in 23 FMF patients aged  $\leq 55$  years.

Diagnosis	Number of patients
Ischaemic heart disease.	12
CVA or TIA	8
Ischaemic heart disease plus cerebral stroke	2
Constriction of renal arteries	1

CVD: cardiovascular disease; FMF: familial Mediterranean fever; CVA: cerebrovascular accident; TIA: transient ischaemic attack.

most severe form of FMF (30). Based on this information we assumed that the fraction of patients manifesting a severe disease in the FMF-CVD cohort would be at least about 70-75% (we used 72.5%). Based on these assumptions,  $\alpha=0.05$  (1-sided), and  $\pi=0.80$ , the minimal sample size was determined at 23 patients, using G\*POWER 3.1.9.2.

## Results

The FMF-CVD group comprised 23 FMF patients,  $\leq 55$ -years old, who were admitted to our centre for an acute CV event over a 15-year period, starting on January 2000. Forty consecutive FMF patients, who were unaffected by CVD, were enrolled to serve as the control group. In the FMF-CVD group, only one patient did not have a detectable

traditional risk factor. This patient had mild FMF, as per Mor SS-2 criteria, and was admitted with an acute myocardial infarction at age 49 years. Additional features of this patient's disease are detailed in Table II. The other 22 patients with CVD had one or more traditional CV risk factors, which could have underlain their CVD.

The distribution of CVD types in all 23 patients is detailed in Table III. The 14 patients with ischaemic heart disease underwent angiography. They all had one vessel disease. Eight had a complete vessel occlusion. Six had  $>70$  and  $<99\%$  stenosis. In all the lesion spanned to a length of  $<1$  cm. In 2 patients, an episode of cerebral stroke has occurred less than 1 week apart from the cardiac episode. In 2 other patients the cardiac episode recurred at an age  $<55$  years with complete occlusion in one patient and stenosis  $>70\%$  in the other one. Both had an additional stenosed artery at the second episode (2 vessel disease), with an atheroma larger than one cm. Ten patients had CVA or TIA, as defined in methods, of which 2 had cardiac episode as well (noted above). One patient with TIA underwent carotid endarterectomy for  $>80\%$  stenosis. Two of the 10 patients had recurrent TIA episodes. The one patient with renal artery stenosis underwent renal artery angiography and insertion of a stent.

Univariate analysis comparing characteristics of FMF patients with and without CVD (Table IV) revealed that the FMF-CVD patient group had a higher proportion of men (78 vs. 40%,  $p=0.005$ ) and higher rates of diabetes mellitus (31 vs. 7%,  $p=0.016$ ) and other inflammatory diseases (30 vs. 7%,  $p=0.005$ ). The mean number of traditional CV risk factors per patient was also higher in this group ( $2.8 \pm 1.2$  vs.  $1.9 \pm 0.8$ ,  $p=0.002$ ). Inflammatory comorbidity included Behçet's disease (3 patients), ankylosing spondylitis (2 patients) psoriatic arthritis (1 patient) and anti-phospholipid antibody syndrome (1 patient) in the FMF-CVD group and Behçet's disease (3 patients) in the control group. There were no differences between the groups with regard to FMF disease severity, mean colchicine dose,

**Table IV.** Potential CV risk factors in FMF patients ≤55 years with CVD.

Parameter	FMF-CVD (n=23)	FMF – controls (n=40)	p-value
<b>Male sex - n (%)</b>	18 (78)	16 (40)	<b>0.005</b>
Severe FMF - n (%)	12 (52)	19 (47)	0.150
Colchicine dose ≥2 mg/day - n (%)	9 (39)	16 (40)	0.877
Colchicine dose, mg/day (mean±SD)	1.4 ± 0.6	1.6 ± 0.6	0.175
M694V/M694V - n (%) <sup>‡</sup>	4 (40)	8 (25)	0.36
Any homozygous or compound heterozygous MEFV genotype - n (%) <sup>‡</sup>	5 (50)	18 (56)	0.73
M694V / non- M694 - n (%) <sup>‡</sup>	5 (50)	18 (56)	0.73
Hypertension - n (%)	13 (57)	23 (57)	0.977
Smoking - n (%)	12 (52)	10 (25)	0.164
Hyperlipidemia - n (%)	13 (57)	15 (37)	0.140
<b>Diabetes Mellitus - n (%)</b>	7 (31)	3 (7)	<b>0.016</b>
Obese (BMI ≥30 kg/m <sup>2</sup> ) - n (%)	0 (0)	5 (12)	0.107
<b>Mean number of CV risk factors per patient (N ±SD)</b>	2.8 ± 1.2	1.9 ± 0.8	<b>0.002</b>
<b>Additional inflammatory diseases - n (%)<sup>*</sup></b>	<b>7 (30)</b>	<b>3 (7)</b>	<b>0.005</b>
Age at episode or recruitment (years ±SD)	47.8 ± 5.65	47.7 ± 8.18	0.948
Severe FMF or colchicine ≥2 mg/day or both - n (%)	12 (63) <sup>‡</sup>	21 (52)5%	0.98

CV: cardiovascular; CVD: cardiovascular disease; FMF: familial Mediterranean fever; MEFV: Mediterranean fever gene; SD: standard deviation.

\*Additional inflammatory diseases: Behçet's disease (3 patients), ankylosing spondylitis (2), psoriatic arthritis (1) and anti-phospholipid antibody syndrome (1). FMF-controls: Behçet's disease (3 patients).

<sup>‡</sup>Genotype evaluation was tallied in 10 FMF-CV and 32 controls, in whom genetic data was available/performed. Also, the severity was determined in 19 FMF-CVD patients versus all 40 controls, in whom all data to compute severity was available. For all other parameters, the number of patients analysed appears in the headings of the columns. Percent of patients is rounded.

the number of patients with colchicine dose ≥2 mg/day and the number of patients with severe FMF or colchicine dose ≥2 mg/day or both. None of the patients on both groups received interleukin 1 blocking agent or another biologic medication. The patients of both groups shared also comparable MEFV genotypes, particularly with regard to the M694V allele.

Multivariate analysis revealed that after adjustment for all 5 covariates (diabetes mellitus, men sex, comorbidities, colchicine dose, disease severity), only comorbidity with other inflammatory diseases (OR 15.1, 95% CI 2.0 – 114.4,  $p=0.036$ ) and diabetes mellitus (OR 13.7, 95% CI 2.1 – 88.5,  $p=0.024$ ) were independent factors associated with the occurrence of CVD in FMF. In this cohort of FMF patients, CVD was not found to be associated with the severity of FMF or with the colchicine dose.

## Discussion

In this study, we analysed CVD admissions of young (aged ≤55 years) FMF patients to a tertiary hospital. Over a period of 15 years, there were only 23 CVD admissions of such patients. Compared to the 40 age adjusted FMF

control subjects, FMF-CVD patients did not have a more severe disease, or required a higher dose of colchicine to control their disease. In contrast, the CVD in FMF was found to be associated with traditional CV risk factors. Compared to FMF patients without CVD, the FMF-CVD group comprised higher proportions of men (78 vs. 40%,  $p=0.005$ ), patients with diabetes mellitus (31 vs. 7%,  $p=0.016$ ), and patients with inflammatory diseases in addition to FMF (30 vs. 7%,  $p=0.005$ ). Patients with FMF-CVD had a higher mean number of traditional CV risk factors per patient (2.8±1.2 vs. 1.9±0.8,  $p=0.002$ ). Of these, comorbidity with other inflammatory diseases (OR 15.1, 95% CI 2.0 – 114.4,  $p=0.009$ ) and diabetes mellitus (OR 13.7, 95% CI 2.1 – 88.5,  $p=0.006$ ), remained independent factors. Contrasting with previous reports on other inflammatory diseases (e.g., RA), the inflammation of FMF, in colchicine-treated patients, does not appear to be involved in the occurrence of CVD.

This study joins the surprisingly sparse literature of the actual occurrence of CVD in FMF, which consists of only 3 studies (18–20). Of these, only one fo-

cused directly on this topic (18), yet all reached the same conclusion: that there is no increased CV morbidity in FMF. The strategy employed in the current analysis was different from that used earlier. Here, we analysed the outcome (already existing CVD in FMF), and explored the possibility that it will be featured by higher degree of inflammation compared to unaffected FMF patients. Yet, even the current strategy, failed to discern a link between FMF-related inflammation and CVD.

Other measures used in current analysis to increase the possible impact of inflammation across other risk factors in predisposing for CVD in FMF was the young age of the patients and the severity of the CV disease using hospital admission as an inclusion criterion. Despite these measures, neither increased FMF severity, nor higher colchicine dose characterised the FMF-CVD group. These findings are in sharp contrast to those for RA where the occurrence of CVD was associated with younger age of patients and higher disease burden (31, 32).

Carriage of the M694V allele is usually associated with a more severe and highly inflammatory phenotype (30, 33). Moreover, increased rate of the M694V allele was found in young Sicilians, (not FMF patients), presented to the hospital with acute myocardial infarction (34). Yet, no increased rate of this allele, neither in homozygous nor in heterozygous forms, was found in our FMF-CVD group, suggesting, also from the genetic perspective that the underlying mechanism for CVD, despite occurring in FMF patients, is not increased inflammation. This finding commensurate with the above finding that traditional risk factors rather than FMF associated inflammation determined the occurrence of CVD in our FMF-CVD group

The observation that comorbidity with other inflammatory diseases appears to be associated with CVD in FMF (Table IV), suggests that CV protection applies specifically to the inflammation generated by FMF. Thus, our findings support the possibility that CV protection in FMF may be driven by colchicine (usage, not dosage), which is uni-



versally and specifically consumed by all FMF patients. Thus, we speculate that non-compliance with colchicine treatment could have underlain the occurrence of myocardial infarction in the one patient in our series for whom no obvious CV risk factors were found. Similarly, non-compliance, under-treatment and resistance to colchicine could have contributed to CVD in other patients published elsewhere (35-37). However, the occurrence of CVD in the FMF-CVD group, despite use of colchicine in a dose similar to that of the control group (Table IV), suggests that colchicine anti-inflammatory protection is quite limited. In addition, non-inflammatory factors not affected by colchicine such as Behçet's vasculitis and thrombophilia of the antiphospholipid antibody syndrome could have a role.

Several lines of evidence support a role for colchicine in CV protection. In a meta-analysis of 15 randomised control trials, Verma *et al.* found that colchicine is effective in secondary prevention of CVD (38). Similarly, Solomon *et al.* suggested that a disparity among gout patients in the use of colchicine might underlie the reduced rate of CVD in those treated with colchicine (39). In the current study, uni- and multivariate analysis failed to show a protective effect for colchicine. However, in a recent study, we exhibited a significant direct association between colchicine dose and the degree of aortic elasticity, a marker of latent atherosclerosis (40).

#### Study limitations

##### – Retrospective design

Since a prospective analysis of FMF patients hospitalised with CVD events would require long-term longitudinal follow-up in a very large FMF population, the retrospective design applied herein seems justifiable, though not optimal.

##### – Cohort size

The cohort of patients with FMF and CVD is small. Nonetheless, the number of patients concurred with the sample sizes computed to obtain meaningful results.

##### – Disease severity as a marker of inflammation

We considered the severity of FMF as a non-direct correlate of inflammation. However, disease severity is assessed according to parameters that reflect inflammation, such as frequency of attacks, the number of sites involved, the duration of attacks and colchicine dose (29). In the absence of long-term reliable markers that reflect inflammation, FMF severity seems to be a reasonable marker of prolonged inflammation. Severe FMF has been shown to correlate well with other markers of inflammation (41-43).

##### – Duration of study period

Some patients were enrolled to the study 15 years apart of each other. However, over 15 years no major development in FMF, relevant to the current study, has occurred. Only at the end of the study period biologics have emerged, but none of the patients in this study received biologic treatment. Therefore the time interval has no effect on the analysis of the FMF-related parameters. In contrast, improved diagnosis of CVD, which has evolved over this period, reduces the possibility that the control population is "polluted" with patients with undiagnosed CVD.

#### Conclusions

Patients with FMF-CVD do not appear to have more FMF related inflammation than FMF patients without CVD, but rather endure more traditional risk factors, of which the most significant are diabetes mellitus and additional inflammatory comorbidities.

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