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Carotid intima-media thickness, lipid profile, serum amyloid A and vitamin D status in children with familial Mediterranean fever

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ABSTRACT

Aim of the work: It was to estimate the carotid intima-media thickness (CIMT), lipid profile, serum amyloid A and vitamin D in Familial Mediterranean Fever (FMF) patients and to explore the relationship between CIMT and FMF.

Patients and methods: The study comprised forty-five FMF patients diagnosed during the attack free period and 40 healthy children with similar demographic features as control. The diagnosis of the FMF cases was confirmed by clinical, laboratory assessments and confirmed by the molecular diagnosis. The CIMT, lipid profile, complete blood picture, serum amyloid A (SAA) levels, vitamin D and the growth pattern were investigated.

Results: The study showed no significant difference of CIMT among patients and controls, significant decrease of vitamin D levels, while lipid profile parameters, triglyceride (TG) to HDL-Cholesterol (HDL-C) ratio, serum amyloid A were significantly increased. A significant correlation was present between the CIMT with the serum cholesterol, low density lipoprotein and triglycerides as well as between SAA and the number of attacks. In addition, vitamin D levels showed significant negative correlation with colchicine. *M694I* mutation was the most prevalent among FMF patients. Growth parameters were normal in FMF cases.

Conclusion: This study sheds light that the normal CIMT in the FMF patients makes it difficult to describe the children as having subclinical atherosclerosis although the higher TG/HDL ratio reflects their risk of atherosclerosis. Moreover, significant decrease of vitamin D in FMF patients was observed. The growth parameters of the FMF patients on regular treatment of colchicine were not affected.

1. Introduction

Familial Mediterranean Fever (FMF) is a hereditary autosomal recessive autoinflammatory illness with a universal prevalence but is predominantly prevalent in the Turks, Armenians, Arabs, and Jews [1]. The diagnosis is assured clinically then by the identification of the mutation in the *MEFV* gene; located on the short arm of chromosome 16 [2]. There are more than 300 mutation variants located on the *MEFV* gene [3]. *M694V* was found to be the most common mutation [2,3]. FMF is characterized by repeated self-limited attacks of fever, inflammation of the peritoneum, joints, pleura, and erysipelas-like erythema [4].

The clinical episodes are associated with increase level of erythrocyte sedimentation rate (ESR) and acute phase reactants as C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen [4]. These laboratory markers usually become normal in between the attacks [5]. Subclinical inflammation may proceed in between the attacks and can cause amyloidosis [6] that may lead to terminal renal disease [7]. Amyloidosis is not always linked to the progression of the illness, as it may happen in patients with simple and infrequent episodes and may occur in patients with no symptoms.

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However, high estimates of SAA for long duration must be present for the amyloidosis to happen [8].

Colchicine is the drug of choice in the treatment of FMF; it is efficient in stopping the episodes in 60–70% of the cases. Chronic inflammation, immune and cholesterol dysregulation play a great role in atherosclerosis [9,10]. In addition, there is an association of cholesterol metabolism with inflammation [11]. Triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C) ratio has been used as an easy reliable way to demonstrate insulin resistance and cardiometabolic risk in normal children [12]. The increase of TG/HDL-C ratio can highly indicate the increasing possibility of having myocardial infarction [13]. The role of TG/HDL-C ratio in producing atherosclerosis in cases with chronic inflammatory disease (CID) remains a debate [14,15]. However, the relationship between carotid intima-media thickness (CIMT) and FMF remains controversial.

The aim of the present work was to estimate the CIMT, lipid profile, SAA and vitamin D levels in FMF patients and to explore the relationship between CIMT and FMF.

2. Patients and methods

This study investigated 45 children diagnosed as FMF [4] during the attacks free period (AFP). The control included 40 normal children, age and sex matched, with similar demographic features, normal physical examination and without any symptoms or signs of active infection or chronic disease. The diagnosis of the FMF patients was based on the history of consanguinity or similarly affected family members, clinical examination according to a severity score performed for each patient [16], and assigned to mild, moderate and severe laboratory investigations were then confirmed by molecular diagnosis of the *MEFV* gene mutations. Patients with any infection, pre-existing illnesses, such as chronic lung diseases, cardiac diseases, diabetes mellitus, hepatic insult, and infectious diseases were excluded. The samples were collected after obtaining the patients or guardians' informed consent using a form approved by the Ethical Committee of the National Research Centre.

All patients and controls were subjected to careful history taking and physical examination. Furthermore, the frequency of attacks, how long it stays, the colchicine dose and presence of co-morbid diseases was enquired.

The weight was measured using a calibrated digital scale to the nearest 0.01 kg, height was measured to the nearest 0.1 cm using Harpenden Stadiometer appropriately by the same person. Body mass index (BMI) was calculated as weight (kg)/height (m2). Z scores of body weight, height and BMI were calculated. All these measurements followed the method of international biological program [17].

Blood samples were collected after a 12-h overnight fast and stored at −80 °C until evaluated. An Olympus AU400 automatic analyzer (Olympus Corporation, Tokyo, Japan) was used to estimate serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG). Low density lipoprotein cholesterol (LDL-C) was calculated according to certain equations (LDL- C) = Total cholesterol − Triglycerides/5 + HDL-C [18].

Complete blood picture was assessed by CELLDYN, neutrophil to lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil counts with the absolute lymphocyte counts, obtained from the differential white blood cells (WBC) count and platelet lymphocyte ratio (PLR). SAA level and serum level of 25-(OH) D were estimated by enzyme-linked immunosorbent assay (ELISA) kits [19,20].

DNA Extraction: Genomic DNA was isolated from peripheral blood samples that had been collected into EDTA-anticoagulated tubes, using (ABIOpure™ total DNA Extraction kit, USA).

PCR amplification and Sequencing: For all patients, both MEFV exon 2 and 10, which are considered as mutation hot spots were individually amplified by PCR using 2 pairs of corresponding primers: Exon 2: F: 5′- GCCTGAAGACTCCAGACCACCCCG-3′,R: 5′AGGCCCTCCGAGGCCTTCTCTCTG-3′,Exon10: F:5′- GAGGTGGAGG TTGGAGACAA-3′, R: 5′- TGACCACCCACTGGACAGAT-3′ [21].

The mean CIMT in the patients and control was assessed using a non-invasive colour coded duplex ultrasound examination by Siemens Acuson S3000 equipment at the ultrasound unit, National Research Centre, Cairo, scanning the carotid system from the most proximal common carotid artery segment to the internal carotid artery.

Statistical analysis: Data analysis was performed with Statistical Package for the Social Sciences (SPSS) 16. Results were expressed as mean ± standard deviation (SD). The Mean values of the groups were compared with the Student *t*-test. The correlation was assessed using the Pearson test (r). $p < 0.05$ was considered significant.

3. Results

The mean age of the 45 patients was 4.85 ± 3.69 years (4–14 years) and were 19 males and 26 females (male: female ratio 1:1.37). The disease duration was 4.32 ± 3.27 years. The 40 controls were of matched age (4.54 ± 3.54 years) and gender (M: F) (0.67 and p = 0.66 respectively). The clinical course of the disease was not affected by the gender of the patients. The frequency of mutations in FMF cases is presented in Table 1. M694I mutation was the most frequent among patients. Characteristics of the patients and controls are presented in Table 2. The children were receiving non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine at a dose of 0.5–2 mg/day. Correlations of the CIMT with the laboratory parameters are presented in Table 3. There was a significant correlation between SAA and the severity of the attacks (r = 0.76, p = 0.0001) and an inversely relation between vitamin D and the colchicine dose (r = −0.56, p = 0.01) in FMF patients as well as between CIMT and disease duration (r = 0.46, p = 0.033 and age (r = 0.58, p = 0.051).

4. Discussion

Atherosclerosis and cardiovascular illnesses are serious etiologies of morbidity and mortality in FMF patients [22]. Systemic inflammation leads to endothelial dysfunction, which causes oxidative stress, vascular damage and finally atherosclerosis [23]. In this work, there was an increased frequency of the *M694I* genotype in children with FMF compared to other genotypes which agreed with a previous study [24]. The results of the z-scores of anthropometric measures in the FMF cases were within the normal range. This coincides with a recent published research [25].

The CIMT is a convenient, easy, and cheap indicator for evaluating cardiovascular risk by estimating the total thickness of the intima and medial layers of the arterial wall [26]. Interestingly, the current study declared no significant difference of CIMT among patients and control which agreed with the research done by *Sari*

Table 1
The frequency of mutations in familial Mediterranean fever (FMF) children.

Mutations n (%)	FMF patients (n = 45)
M694I	33 (73)
M680I	9 (20)
V726A	3 (7)

FMF: Familial Mediterranean Fever.

Table 2
Characteristics of familial Mediterranean fever (FMF) patients and controls.

Parameter mean ± SD	FMF patients (n = 45)	Controls (n = 40)	p
Age (years)	4.85 ± 3.69	4.54 ± 3.54	0.67
Gender M:F	1:1.37	1:1.36	0.66
Dis. Dur. (years)	4.32 ± 3.27	–	–
Weight (kg)	25.4 ± 8.4	25.6 ± 7.4	0.71
Height (cm)	118.5 ± 9.4	119.1 ± 10.5	0.68
BMI (kg/m^2)	16.2 ± 2.8	16.3 ± 2.8	0.96
Mean CIMT	0.051 ± 0.01	0.047 ± 0.004	0.29
vitamin D (ng/ml)	25.7 ± 12.6	41 ± 7.7	**0.001**
Cholesterol(mg/dl)	115.1 ± 14.3	100.9 ± 5.4	**0.001**
HDL-C (mg/dl)	41.3 ± 6.7	56.5 ± 5.22	**0.001**
LDL-C(mg/dl)	51.3 ± 14.9	29.13 ± 7.07	**0.001**
TG (mg/dl)	112.6 ± 33.9	76.8 ± 8.24	**0.001**
TG /HDL-C ratio	2.83 ± 1.08	1.37 ± 0.19	**0.001**
NLR	1.35 ± 0.75	1.04 ± 0.4	0.32
PLR	5.9 ± 2.6	5.8 ± 1.11	0.79
SAA mg/L	1.5 ± 0.51	0.99 ± 0.06	**0.001**

FMF: familial Mediterranean fever; Dis.Dur.: disease duration; BMI: body mass index; HDL-C:high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; NLR: neutrophil to lymphocyte ratio; PLR: platelets to lymphocyte ratio; SAA: serum amyloid A. Bold values are significant at $p < 0.05$.

Table 3
Correlation of the carotid intima-media thickness (CIMT) with lipid profile, vitamin D level and serum amyloid A (SAA) in familial Mediterranean fever (FMF) patients.

Parameter r (p)	CIMT in FMF patients (n = 45)
Age (years)	0.58 (0.051)
Dis. Dur. (years)	0.46 (**0.033**)
Cholesterol (mg/dl)	0.48 (**0.012**)
HDL-C (mg/dl)	−0.29 (0.15)
LDL-C (mg/dl)	0.4 (**0.038**)
TG (mg/dl)	0.4 (**0.037**)
Vitamin D (ng/ml)	−0.22 (0.39)
SAA (mg/L)	0.45 (**0.035**)

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; SAA: serum amyloid A. Bold values are significant at $p < 0.05$.

et al., [27]. On the other hand, *Akdogan et al.*, [28] and *Ugurlu et al.*, [29] reported that the mean CIMT in patients was higher than the controls. This could be due to the fact that CIMT requires more time to be affected by subclinical inflammation as the present cases were younger in age.

Several researchers suggested that low vitamin D is the consequence of chronic inflammation [30] as it stops the production of interleukin (IL)-6 and interferon-γ and acts as an immune-modulatory role [31]. Osteoporosis in patients with FMF can also be related to vitamin D deficiency [32]. In this work, FMF patients had significantly lower vitamin D than control. This is in agreement to another study [33].

In the present study, patients with FMF developed significant higher level of cholesterol, triglycerides, LDL-C and significantly lower HDL-C compared to the control. A lower HDL-C and higher triglyceride levels has been reported in FMF patients than in healthy children [34]. In a recent study, higher triglyceride and lower HDL-C serum levels were found in FMF patients compared to healthy subjects [35], suggesting that the differences in HDL-C and triglyceride levels can be associated with the inflammation and increased possibility of having atherosclerosis in FMF subjects. In the present study, high significant difference was found between cases and controls regarding the triglyceride/HDL-C ratio, which agrees with others [14]. TG/HDL-C ratio is a simple, valuable indicator of atherosclerosis and a strong indicator of coronary artery disease [36].

The NLR showed no significant increase among patients which corroborates with a previous study that emphasized no significant difference in the NLR in the cases [37]. These findings disagreed with another study which showed significant difference among patients and control [38]. This discrepancy may be due to difference in the degree of severity or ethnicity. The detection of a high NLR in children suffering from FMF, indicates that subclinical inflammation in FMF continues during the attack-free periods [39]. Accordingly, there is a risk for amyloidosis in untreated patients and in those who do not regularly use the colchicine drug. This work showed no significant difference in PLR among patients and control which is in disagreement to the findings of another study which delineated high significant difference among patients and controls [37].

In the current study, SAA was significantly higher in patients than controls and correlated with the severity of the attacks in FMF cases [37]. Moreover, there was no correlation between the CIMT and SAA which agrees with another study [37] while on the other hand, another work showed that amyloidosis correlated with the CIMT [40]. This may be due to difference in age of patients. A negative correlation was found between vitamin D level and colchicine dose which is in accordance to the findings of a previous work [33]. Defects in the microtubular network due to colchicine treatment can decrease serum vitamin D levels due to raised level of 1,25 (OH) vitamin D and 24,25 (OH) vitamin D [33]. Some researchers linked low vitamin D levels to malabsorption of the vitamin as a result of colchicine treatment [32].

The limitations of the study include the small sample size, lack of correlations between the CIMT and the clinical manifestations and absence of a longitudinal design.

In conclusion, this study sheds light on the limited reliability of CIMT for the detection of atherosclerosis in FMF patients; however, higher TG/HDL ratio might better reflect raised atherosclerotic possibility. Moreover, significant decrease of vitamin D in FMF patients was observed. The growth parameters of the FMF patients on regular treatment of colchicine were not affected.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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