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The relationship between nutrition, inflammation and colchicine resistance in familial Mediterranean fever

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ABSTRACT

Aim: Familial Mediterranean fever (FMF) is an autoinflammatory and genetic disease associated with chronic inflammation. Colchicine is the gold standard treatment for FMF, although some patients respond partially. Factors such as heavy exercise, cold exposure, stress, recent infection or surgery have been associated with the occurrence of attacks. Recently, nutrition is thought to be involved in the pathogenesis of autoimmune and autoinflammatory diseases. Therefore, we aimed to investigate the relationship between nutrition, inflammation and colchicine resistance by considering the nutritional status of FMF patients.

Material and Method: The study included 59 patients and 67 healthy individuals who were matched for gender, age and body mass index (BMI). Clinical, anthropometric, and biochemical measurements were obtained. Three-days, 24-hour diet records were recorded in the nutrient database program (BeBiS software program), the amounts of macro and micronutrient contents were determined and the Diet Inflammatory Index (DII) score was calculated and compared between groups.

Results: Statistically, the diets of FMF patients were found to be higher in omega-6, carbohydrate percentage and salt content, and lower in terms of lactose, fat percentage, monounsaturated fatty acids, retinol and biotin compared to controls. There was no correlation between DII and acute phase reactants and colchicine dose.

Conclusion: The course of FMF can be affected by environmental factors, as well as its genetic background. Nutrition is a new and interesting topic in this regard and may contribute to inflammation and disease activity in FMF patients.

Keywords: Familial Mediterranean fever, inflammation, nutrition, colchicine resistance, dietary inflammatory index

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by recurrent fever and serosal inflammation in the peritoneum, lungs and joints. The first attack usually occurs in childhood. Attacks usually develop within a few hours and last 6-72 hours (1). FMF is common in people of Mediterranean and Middle Eastern origin and a study conducted in Turkey has shown that the prevalence of FMF is 1 in 1000. It is an autosomal recessive disease and the MEFV gene (16 p13.3) located on the short arm of chromosome 16 is responsible for the disease. FMF presents with recurrent episodes of fever and serositis that cause severe abdominal, chest, and joint pain. Although the attacks resolve spontaneously, the goals of treatment are to prevent attacks and amyloidosis, and to reduce subclinical inflammation (1).

Colchicine blocks cytokine release and microtubule polymerization, suppresses inflammation and prevents the development of amyloidosis (2). However, approximately 30-40% of patients respond partially to colchicine treatment, and 5% of these appear to be colchicine resistant (3). Although 'colchicine resistance' is not clearly defined in the literature, most commonly considered to mean more than 4 attacks in the last 6 months or more than 6 per year.

FMF is associated with chronic low-grade inflammation, and dietary components are known to influence the state of chronic low-grade inflammation. The Dietary Inflammatory Index (DII) is a literature-based scale developed to assess the potential effect of diet on inflammation. High DII score is associated with pro-inflammatory, low DII score is associated with anti-inflammatory status. The index was developed by

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reviewing a wide variety of publications and serves to assess the relationship between various dietary components and inflammatory biomarkers [tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interleukin (IL)-1β, IL-4, IL-6, IL-10] (4). In the literature, high DII scores have been found to be associated with diseases accompanied by inflammation such as obesity, cardiovascular diseases, rheumatoid arthritis and cancer (5-7).

Factors such as severe stress, heavy exercise, cold exposure, recent infection and surgery and menstrual periods have been associated with the occurrence of attacks. Recently, the issue that diet has an important role in the etiopathogenesis of autoimmune diseases has been on the agenda (8,9). In addition, it has been shown that functional gastrointestinal disorders are more common in patients with FMF in recent years (9). However, studies examining the effect of nutritional habits on symptoms and treatment outcomes in FMF patients are lacking in the literature. Therefore, we aimed to investigate the relationship between nutrition, inflammation and colchicine resistance by comparing the nutritional status of FMF patients and healthy controls.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: E1-22-2320). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. We obtained written informed consent from each participant.

Study Population

This is a cross-sectional study including 59 adult FMF patients diagnosed according to Tel-Hashomer criteria and 67 healthy individuals. Those with chronic drug use other than colchicine and those with a diagnosis of chronic disease were not included in the study.

The demographic characteristics of the participants, body mass index (BMI), age at first symptom in FMF patients, age at diagnosis, clinical features of FMF, treatment content, family history of FMF, comorbidities, frequency of attacks, and sedimentation and CRP results at last visit were recorded.

We measured the participants' height using an unstretched meter while standing with their shoulders against the wall in a normal position. We measured their weight with a portable digital scale. BMI was calculated by dividing the body weight by the square of the height (kg/m²) as standard. Over at most single layer of lightweight clothing, we measured waist circumference (WC) at the umbilicus level

Attack Definition and Colchicine Resistance in FMF Patients

FMF attack was defined as fever lasting 6-72 hours (≥ 38°C) with serositis/arthritis/skin rash and elevated CRP (> 5 mg/L) and/or erythrocyte sedimentation rate (ESR) (> 20 mm/h). Colchicine resistance was defined as more than three typical attacks in last six months despite using 2 mg or more of colchicine (10). Patients who were not compliant to the colchicine treatment were excluded.

Dietary Assessment

Participants were asked to keep a record of the amount and content of the foods they consumed for three days. The days had to include two weekdays and one weekend day with normal eating habits. The participant was given both written and verbal instructions by his/her physician about recording the diet. Data regarding three-day and 24-hour diet was recorded in the licensed nutrient database program (BeBiS software program) by the same dietitian, and the average amounts of macro and micronutrient contents of the participants were determined (11).

Calculation of DII Score

DII is an index calculated on 45 nutrients and food components thought to have a potential effect of diet on the inflammatory state. In DII calculation, the Z-score values [(individual's daily food consumption/nutrient-standard global consumption amount)/food/nutrient standard deviation value] were calculated from the daily food/nutrient intakes of each individual and then converted to percentage points. To obtain a symmetrical distribution, each percentile was doubled and then "1" was subtracted. The centralized percentage values determined for each food/nutrient were multiplied by the "individual full inflammatory effect score" (4). 33 of the 45 possible foods/nutrients were used to calculate the DII from the food consumption records of the participants [energy (kcal), protein (g), total fat (g), saturated fat (g), monounsaturated fatty acids) (g), polyunsaturated fatty acids (g), n-3 fatty acid (g), n-6 fatty acid (g), cholesterol (mg), carbohydrate (g), fiber (g), caffeine (mg), vitamin a (μgr), beta carotene (μgr), vitamin d (μgr), vitamin e (mg), thiamine (mg), riboflavin (mg), niacin (mg), vitamin b6 (mg), folic acid (μgr), vitamin b12 (μg), vitamin c (mg), iron (mg), magnesium (mg), zinc (mg), selenium (μgr), green/black tea (g), onion (g), garlic (g) , pepper (g), thyme (mg), ginger (g)].

Statistical Analysis

SPSS software (version 18; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate the homogeneity of the distribution of the continuous variables. Continuous variables which were not normally distributed were presented as medians (interquartile range [IQR]).

Categorical variables were analysed using χ2 test and presented as numbers. Continuous variables were compared between groups by using the Mann-Whitney U test in absence of normal distribution. Correlations between variables were analyzed using Spearman's rank correlation coefficients. A p value lower than 0.05 was considered significant. The power of the study was 87% with the current sample size using the G power program (12).

RESULTS

FMF and control groups were similar in terms of age (34 (24-43) vs. 35 (31-44), p= 0.087) and gender distribution (37 females, 22 males vs. 52 females, 15 males, p=0.067). There was no difference between the groups in terms of waist circumference, hip circumference and DII scores. Demographic characteristics and statistically different nutritional contents of all participants are presented in **Table 1**. Other than those in this table, no difference was found between the two groups in terms of all nutritional contents (vitamins, minerals, fatty acids, amino acids etc.) and it was not presented as a separate table as it would take too much space to write each.

Table 1. Demographic characteristics and statistically different nutritional contents of all participants

	FMF (n=59)	Controls (n=67)	p*
Gender	37 Female. 22 Male	52 Female. 15 Male	0.067
Age,yr	34 (24-43)	35 (31-44)	0.087
BMI,kg/m²	24.33 (20.38-29.08)	25.27 (22.67-29.47)	0.28
WC, cm	78 (84-97.5)	89 (80-99)	0.676
DII Score	0.06442 (-0.57932-0.61408)	0.07386 (-0.73262-0.71378)	0.997
Carbohydrate, %	51 (45-54)	45 (40-48)	<0.001
Carbohydrate, gr	241.3 (167.9-269.2)	189.8 (149.4-233.8)	0.051
Lactose, gr	4.6 (1.9-8.4)	6.4 (3.3-9.9)	0.05
Fat, %	36 (31-40)	39 (36-43)	<0.001
Fat, gr	68.6 (54.4-89.4)	76.3 (66.1-92)	0.072
Cholesterol, mg	209.4 (122.2-313.2)	297.1 (204.1-424.9)	0.005
Omega-6, g	19.9 (16-27)	17.9 (9.5-25.3)	0.04
Omega-6/Omega-3	15.11 (11.58-20.18)	14.90 (10.49-19.80)	0.599
Retinol, µgr	265 (190-385)	368.8 (255.4-515.3)	0.03
Biotin, µgr	31.6 (25-44)	41.2 (31.9-48.2)	0.014
Sodium,mg	4008.9 (3218.5-5043.4)	3356 (2687.1-4132)	0.02
Chloride, mg	6160.7 (4976.7-7632.2)	4802.3 (4015.5-6163.1)	0.001
Salt, gr	9.7 (7.7-12.1)	7.5 (6.3-9.6)	0.001
Iodine,µgr	161.7 (123.9-220.7)	132.2 (103.9-176.5)	0.013

BMI; body mass index; FMF, Familial Mediterranean fever; WC, waist circumference; DII, dietary inflamatuar index p* <0.05 denoted as statistically significant (in bold), Mann-Whitney U test Values are expressed as median (interquartile range)

The median age of first symptom of FMF patients was 15 (7-23), the median age of diagnosis was 23 (15-32) and the general characteristics of their diseases are given in **Table 2**.

Table 2. General disease characteristics of all FMF patients

n=59	Positive (n)	Negative (n)
Resistance	22	37
FMF symptoms		
Fever	57	2
Peritonitis	57	2
Pleuritis	12	47
Arthritis	15	44
Erysipelas	7	52
Pericarditis	0	59
Vasculitis	3	56
Amyloidosis	10	49
End stage renal disease	5	54
Family history of FMF	35	24

FMF, Familial mediterranean fever, n, number of FMF patients

In addition, a statistically significant difference was found only in terms of dietary lactose in the diet comparison made in terms of groups with and without resistance among FMF patients (5.25 (2.95-15.06) vs. 3.02 (0.89-7.24), p= 0.017), and a difference was found in terms of ESR (17 (7.75-37.5) vs. 10 (5.5-12.5), p= 0.047) and the findings are shown in **Table 3**.

Tablo 3. Dietary comparison between resistant and non-resistant FMF patients

	Resistance positive	Resistance negative	p*
Gender	11F. 11M	26F. 11M	0.12
Age,yr	39.00 (26.7-47.3)	29 (24-37)	0.95
BMI, kg/m²	24.05 (21.22-29.50)	26.23 (20.18-28.97)	0.86
WC,cm	83 (77.25-87)	92 (78-100)	0.34
ESR, mm/h	17 (7.75-37.5)	10 (5.5-12.5)	0.047
CRP, mg/L	4 (1-37.25)	5 (1-11.5)	0.886
DII Score	0.18205 (-0.59867-0.80775	0.06442 (-0.53207-0.58737)	0.88
Colchicine dose, mg	2 (1.38-2)	1.5 (1-1.5)	0.063
Lactose, gr	5.25 (2.95-15.06)	3.02 (0.89-7.24)	0.017

BMI, Body mass index; WC, waist circumference; ESR, erythrocyte sedimentation rate; CRP, C- reactive protein; DII, Dietary inflamatuar index, p* <0.05 denoted as statistically significant (in bold), Mann-Whitney U test, Values are expressed as median (interquartile range)

No correlation was found between DII and demographic characteristics in both groups, as well as acute phase reactants and colchicine dose in the FMF group, and the results are shown in **Table 4**.

Table 4. Correlation results with Dietary inflammatory index

	FMF DII score		Controls DII score	
	r	p	r	p
Age,yr	-0.099	0.465	-0.212	0.143
BMI, kg/m²	-0.131	0.550	-0.035	0.812
WC,cm	0.122	0.652	-0.153	0.316
ESR, mm/h	0.199	0.137	-	-
CRP, mg/L	0.088	0.515	-	-
Colchicine dosage,mg	0.036	0.793	-	-

BMI, body mass index; WC, waist circumference; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein, *Correlation is significant at the ≤ 0.05 level, r correlation coefficient

DISCUSSION

To the best of our knowledge, this is the first study to examine nutritional status in FMF patients to date. In our study, there was no difference between FMF patients and healthy controls in terms of DII scores. The amount of biotin in the diet of FMF patients was found to be significantly lower than in the control group. However, no difference was found between resistant and non-resistant FMF patients. Although the amount of fat was similar to the control group, the percentage of fat was found to be lower in the patient group. However, the groups were similar in terms of dietary protein and carbohydrate content, but the percentage of carbohydrate was found to be higher in the patient group. In addition, there was no difference between resistant and non-resistant FMF subgroups in terms of carbohydrate, fat and protein. While the amount of monounsaturated fatty acids in the diets of FMF patients was lower, there was no difference between the groups in terms of saturated and polyunsaturated fatty acids. However, the groups were similar in terms of omega 3, but omega-6 was statistically higher in the FMF group. Dietary lactose content and retinol content of the patient group were found to be lower than the healthy group. On the contrary, salt intake of the FMF patient group was significantly higher than the control group. Dietary iodine content was significantly higher in favour of the FMF patient group.

FMF is caused by gain-of-function mutations in the gene encoding pyrin (MEFV), a protein found in various isoforms in the cytoplasm or nucleus (13). The role of pyrin in the nucleus is not known exactly. Once activated, pyrin oligomerizes with cellular proteins and activates caspase-1 by forming a macromolecular complex called "pyrin inflammasome". Caspase-1 causes the release of proinflammatory IL-1β and IL-18, resulting in pyroptosis, the inflammatory death of cells. IL-1β contributes to the inflammatory burst by stimulating the expression of genes involved in the IL-1 pathway. Pyrin expression can be upregulated by lipopolysaccharides (LPS) and cytokines such as interferon (IFN)-γ, TNF-α, IL-4 and IL-10. Pyrin is expressed in innate cells, including monocytes, granulocytes, dendritic cells, synovial and serosal fibroblasts. Over activation of the pyrin inflammasome and consequent inflammation triggers the febrile inflammatory episodes, typical of FMF (14).

Diet plays an important role in chronic inflammation and the DII is a scale developed to assess this condition. For example, an inverse relationship between fruit and vegetable consumption and inflammatory markers such as CRP, IL-6 and TNF-α has been shown in the literature (15). In our study, DII scores of FMF and control groups were similar. Despite the high number of patients with colchicine resistance in our study, there was no correlation between ESR and CRP and DII in the FMF group. This result may have been due to our sample size or the predominance of genetic features in the etiopathogenesis.

Biotin is a B-complex vitamin that acts as the main coenzyme for five carboxylases in the body: Coenzyme for pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase 1 and 2. Since these enzymes are involved in various metabolic pathways such as gluconeogenesis, amino acid metabolism and fatty acid synthesis, inflammatory and immunological disorders may accompany biotin deficiency (16). Although the mechanisms of this situation have not been clarified yet, one of the mechanisms that may be related to FMF may be the effect of biotin levels on transcriptional factors such as Nuclear Factor kappa B (NF-κB). It has been shown in the literature that the nuclear abundance and transcriptional activity of NF-κB are significantly higher in biotin-deficient cells than in biotin-supplemented cells (17). In addition, it has been shown that IL-1β and TNF-α increase in biotin deficiency. In the study of Kuroishi et al. (18), TNF-α production in biotin-deficient macrophages was found to be significantly higher than in biotin-sufficient macrophages, and this was down-regulated by biotin supplementation. Wiedmann et al. (19), on the other hand, found that IL-1β, IFN-γ and Ig μ chain in gene expression analysis in concanavalin A stimulated peripheral blood mononuclear cells isolated from healthy adults before or after biotin supplementation for 3 weeks, showed that it was up-regulated after biotin supplementation. Although these seem to be conflicting, the experimental conditions were different. Also it is logical that biotin supplementation would up-regulate IFN-γ. Biotin plays an important role in the maturation and responsiveness of immune cells, the function of natural killer (NK) lymphocytes, and the formation of cytotoxic T lymphocytes. T cell and B cell immunity may be impaired due to biotin deficiency.

Current evidence indicates that biotin has a vital role in chromatin structure and gene expression. Biotin maintains genome stability by binding to histones and playing a role in transcriptional repression of genes (16). In our study, the amount of biotin in the diets of FMF patients was found to be significantly lower than in the control group. However, no difference was found between resistant and non-resistant FMF patients. Based on all these results, we hypothesized that biotin supplementation in order to reduce inflammation in FMF patients may contribute to the clinical improvement.

Recent studies have provided advances in demonstrating the relationship between nutrition/metabolic regulation and immunological/inflammatory functions (20). Immunological responses such as lymphocyte proliferation

and cytokine production are metabolically costly, and nutritional and metabolic conditions are expected to affect immunological function. In 1961, Mellinkoff et al. (21) suggested that a low-fat diet reduces the incidence of fever episodes in patients with FMF and that there is a close relationship between dietary imbalances and exacerbations. In a study a year later, Sohar et al. (22) suggested that a low-fat diet had no effect on attack frequency in FMF patients who had not previously taken colchicine. No other studies have been conducted in subsequent years to elucidate the effect of diet on FMF, and the role of diet in this condition has been underestimated. Although it is accepted that carbohydrates have inflammatory effects in relation to the glycemic index (GI) and glycemic load (GL) of foods, this issue is still controversial in the literature. Hu et al. (23) showed a positive relationship between dietary GI and oxidative stress, and another study showed that high GI carbohydrates increased NF-κB activation (24). It has also been reported that relatively high consumption of both soluble and insoluble fibre is inversely related to IL-6 and TNF-α, but not to CRP levels. Presumably, the inflammatory response may differ depending on the type of carbohydrate (25). In our study, although the amount of fat in the diet of FMF patients was similar to the control group, their fat percentage was found to be lower. Although the amount of dietary protein and carbohydrate was similar between the groups, the percentage of carbohydrates was found to be higher in the patient group. In addition, in the FMF subgroups, no difference was found in terms of carbohydrate, fat and protein. However, since the GI and GL of carbohydrates were not calculated in our study, it is not possible to reach an absolute conclusion on this subject for now, and further studies will be beneficial.

Monounsaturated fatty acids (MUFA), moderately saturated fatty acids (SFA) and polyunsaturated fatty acids (PUFA) have anti-inflammatory activity and have protective effects on the immune-mediated inflammatory response (26). In our study, while the amount of monounsaturated fatty acids was found to be lower in the diets of FMF patients, which may be related to this mechanism, there was no difference between the groups in terms of saturated and polyunsaturated fatty acids.

PUFAs are omega-3 and omega-6 fatty acids. Long-chain omega-3 fatty acids (LCn3) include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish, and alpha-linolenic acid (ALA) found in some vegetable oils (including hazelnuts and peanuts). Many vegetable oils contain omega-6 fats, especially linoleic acid (LA). Omega-6 (LA) has been associated with proinflammatory effects and its derivative arachidonic acid (AA) is a precursor for key proinflammatory mediators, while LCn3 reduces various physiological aspects of inflammation and production of prostaglandin and leukotrienes from omega-6 (27). In our study, although the groups were similar in terms of omega 3, omega-6 was found to be statistically higher in the FMF group. This suggests that adding omega 3 to the diet may be beneficial in reducing inflammation.

After the recognition of inflammation as an important research area in nutritional sciences, dairy products have become a food type that has attracted attention to work in this context. Milk is a natural food that contributes to prebiotics and probiotics acting on immunity, inflammatory processes and microflora. Studies on the effect of dairy products on inflammatory processes have reported conflicting results such as beneficial, ineffective and harmful (28). In a study of various patient groups, the proinflammatory effect of dairy products was determined in people with milk allergies (27). However, a recent systematic review concluded that dairy consumption had no adverse effects on biomarkers of inflammation in overweight and obese subjects (29). Bioactive peptides and glycans derived from bacterial fermentation of milk can interact with both the microbiota and immune cells, contributing to its anti-inflammatory activity (30). In our study, the amount of lactose in the diet of the FMF group was found to be lower than that of the control group. This may be due to either the contribution of lactose deficiency to inflammation or the high prevalence of lactose intolerance in Turkish society, and that patients reduce their milk intake to avoid abdominal discomfort.

Vitamin A is available in forms such as retinal, retinol, and retinoic acids and is an essential micronutrient. Vitamin A in dietary is absorbed from retinoids as retinol or as pro-vitamin A carotenoids, which are converted to retinol in the enterocyte. Vitamin A is an important component of immunity as well as having many functions such as embryological development, cellular differentiation, growth, vision and reproduction. Vitamin A regenerates the mucosal barriers, contributes to the innate immune function by supporting neutrophils, macrophages and NK cells, and its deficiency can impair both innate and adaptive immune functions (31). In our study, dietary retinol levels of FMF patients were found to be lower than the healthy group. Studies are needed to investigate the contribution of vitamin A supplementation to disease activity in these patients.

Salt is an important component of the diet, polarizing adaptive and innate immune cells towards the proinflammatory side and causing partial damage to target organs. Dendritic cells activated by excess sodium increase the production of IL-1β and the T cell cytokines IL-17A and IFN-γ (32). Macrophages are classified into proinflammatory M1 and anti-inflammatory M^2 phenotypes, which play important roles in mediating T helper (Th) 2 immunity, suppressing effector T cell

function, and wound healing. However, NaCl causes blunting of activation of M² macrophages (33). Salt induces proinflammatory cells such as Th 17 and restricts the reparative effects of M1 macrophages and regulatory T cells and M² macrophages. Also critical for the formation of a Th 17 response, the inflammasome can induce widespread inflammatory responses after exposure to a high-salt environment. Studies have shown that excessive salt intake disrupts the balance between immunosuppressive and inflammatory effects and represents an environmental risk factor for the development of autoimmune diseases, arterial hypertension and perhaps other diseases whose associations will emerge in the future (34). In our study, surprisingly, salt intake in the diet of the FMF group was significantly higher than that of the control group. In the future, perhaps, interventional studies will show that salt is a factor that may contribute to increased inflammation in these patients.

Innate immunity related alterations are prominent in the pathogenesis in FMF, whereas adaptive immunity changes are prominent in autoimmune thyroid disease, which is thought to be related to iodine. However, in our study, the dietary iodine content of FMF patients was significantly higher than the healthy group. In addition, there was no difference in terms of iodine between the FMF patients with and without resistance. However, since thyroid function tests (TFT) were not recorded in our study, the effect of the current iodine level on TFT could not be examined.

The limitations of our study are as follows; relatively small sample size, not controlling factors such as retinol, biotin, fatty acids in the serum, not questioning lactose intolerance, not recording thyroid function test results, and not specifying the types of foods. The strength of our study is that it is the first study in the field of nutrition in FMF patients, in which all components of the diet were examined, and the number of patients with colchicine resistance was high.

CONCLUSION

FMF disease can be affected by environmental factors as well as genetic background. Nutrition is a new and interesting topic in this regard. In our study, the diets of FMF patients were found to be higher in omega-6, carbohydrate percentage and salt content, and lower in lactose, fat percentage, monounsaturated fatty acids, retinol and biotin compared to the control group. Our current data suggests that diet may partially contribute to inflammation and disease activity in FMF and future large-scale nutritional intervention studies may further elucidate this issue.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: E1-22-2320).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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