REVIEW
Derleme

# The Effects of Diet and Microbiota on Attacks in Familial Mediterranean Fever

# Ailesel Akdeniz Ateşinde Diyet ve Mikrobiyotanın Ataklar Üzerindeki Etkileri

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## ABSTRACT
Familial Mediterranean fever (FMF) is one of the common autoinflammatory diseases with autosomal inheritance. It is more common, especially in certain European ethnic groups, and is seen frequently in Turks, North Africans, Arabs, Jews, and Armenians. In our country, the prevalence varies between 1/400 and 1/1000. In the pathogenesis, there is a mutation in the MEFV gene, composed of 10 exons and localized at the 16p13.3 chromosome. A 781 amino acid protein is encoded by (pyrine or marenostrin) the MEFV gene and regulates intranuclear peptide transcription when inflammation occurs. Clinically, FMF is characterized by pronounced acute phase response (leukocytosis, high erythrocyte sedimentation rate, C reactive protein, serum amyloid, fibrinogen) accompanied by recurrent fever and symptoms. Although the reasons that stimulate and terminate attacks are not known exactly, several factors such as infection, menstruation, surgical intervention, cold climatic conditions, a high-fat diet, and excessive physical activity can trigger attacks. In a small number of studies, it has been examined that the species that dominates the microbiota of individuals with FMF is also different from the microbiota patterns of healthy individuals. The purpose of this study is to evaluate some factors that affect the attacks' frequency and duration in individuals with FMF, especially diet patterns.

**Key Words:**
Familial Mediterranean fever, Nutrition, Diet

## ÖZ
Ailesel Akdeniz ateşi otozomal geçişli ve en sık görülen otoinflamatuar hastalıklardan birisidir. Özellikle Avrupa kökenli bazı etnik gruplarda daha yaygındır. Türkler, Kuzey Afrikalılar, Araplar, Yahudiler ve Ermenilerde sıklıkla görülmektedir. Ülkemizde ise prevalansı 1/400 ve 1/1000 arasında değişmektedir. Patogenezinde 16p13.3. kromozomda lokalize olan 10 ekzondan oluşan MEFV genindeki mutasyon etkilidir. MEFV geni 781 amino asitlik bir proteini (pirin veya marenostrin) kodlamaktadır ve inflamasyon durumunda intranükleer peptidlerin transkripsiyonunu düzenlemektedir. Klinik olarak Ailesel Akdeniz ateşi, tekrarlayan ateş ve semptomların eşlik ettiği belirgin akut faz yanıtı (lökositoz, yüksek eritrosit sedimantasyon hızı, fibrinojen, C reaktif protein, serum amiloid) ile karakterizedir. Atakları uyaran ve sonlandıran nedenler tam olarak bilinmemekle birlikte enfeksiyon, menstrüasyon, cerrahi girişim gibi çeşitli faktörlerin, soğuk iklim koşulları, yüksek yağlı diyet ve fiziksel aktivitenin normalden fazla olmasının atakları tetikleyebileceği bilinmektedir. Yürütülen az sayıdaki çalışmada Ailesel Akdeniz ateşi hastalığına sahip bireylerin mikrobiyotasında hakim olan türün de sağlıklı bireylerin mikrobiyota örüntülerinden farklı olduğu gözlenmiştir. Bu çalışmanın amacı Ailesel Akdeniz ateşi hastalığına

sahip bireylerin atak sıklık ve sürelerine etki eden başta diyet örüntüsü dahil olmak üzere bazı faktörleri incelemektir.

**Anahtar Sözcükler:**
Ailesel Akdeniz Ateşi, Beslenme, Diyet

## INTRODUCTION

Familial Mediterranean fever (FMF) is one of the common autoinflammatory diseases with autosomal inheritance (1). The pathogenesis of FMF is based on mutations on the MEFV gene, which contains 10 exons that are localized on the 16p13.3 chromosome. A 781 amino acid protein is encoded by (pyrine or marenostrin) the MEFV gene and regulates intranuclear peptide transcription when inflammation occurs. (2). Pyrin play a key role for innate immune system and expressed in neutrophils, eosinophils, equilibrium cells, mature monocytes, and the cytoplasm of synovial fibroblasts (3). Furthermore, in the case of leukocyte infiltration, it has also been detected in the spleen, lungs, liver and muscles (4). Pyrin is localized with microtubules and exhibits potential activity for microtubule activity stabilizing agents, such as colchicine (5).

Clinically, FMF is characterized by a pronounced acute phase response (leukocytosis, high erythrocyte sedimentation rate, fibrinogen, C reactive protein, serum amyloid) that is accompanied by recurrent and self-limiting fever and symptoms. Although the reasons that stimulate and terminate these attacks are not known exactly, it is known that various stress factors such as infection, menstruation, surgical intervention, cold climatic conditions, high-fat diet and excessive physical activity may trigger attacks (6,7). During attacks, there are clinical signs such as peritonitis (95%), arthritis (> 50%), pleuritis (40%), and less frequently pericarditis, scrotal swelling (tunicitis vaginalis testis), myalgia and erysipeloid skin rash. Attacks usually last 2-3 days. Although they starts at the age of 20 (85%), the first attacks are rarely seen older than 50 years of age (8). One of the worrying scenarios with amyloid A protein amyloidosis (AAA) is the progressive secondary form of AA amyloidosis, which comprises a subgroup of patients, at risk for end-stage renal disease (9). This study aimed to examine some factors that affect the frequency and period of attacks of individuals with FMF, especially their diet patterns.

## Epidemiology

FMF is more common, in some ethnic groups of European descent. It is frequently seen among Turkish, North Africans, Arabics, Jewish and Armenian populations (4). In Italy, it is stated that FMF is generally seen in some populations of Jewish-Armenian-Greek origin (10). In Turkey, the prevalence of FMF varies between 1/400 and 1/1000 (11,12). It is known that most of the FMF patients commonly live in central Anatolia, Eastern Anatolia and the Black Sea regions (13,14). FMF is seen more often in men than in women (male / female 1.5-2: 1) (15).

## Other Diseases and Familial Mediterranean Fever

It has been stated in the literature that FMF can be seen together with some other autoinflammatory diseases such as celiac, autoimmune thyroid disease, type 1 diabetes (16,17). It has been stated that progression of FMF with these diseases may delay its diagnosis (16). In Italy, a placebo-controlled 2-week double-blind study was conducted on participants who stated that they had non-celiac gluten sensitivity and AAA as well as healthy participants. The effects of rice and wheat on the clinical progression of the disease were evaluated. In this study, the clinical symptoms were scored using the AAA-specific Auto-Inflammatory Diseases Activity Index (AIDAI), serum amyloid A (SSA), serum soluble CD14 (sCD14), tumor necrosis factor (TNF), C-reactive protein (CRP) and circulating CD14 + monocytes expressing interleukin (IL) -1 levels were analyzed. The AIDAI scores of the FMF patients were significantly higher with wheat consumption, but not with rice. The CD14 levels of the FMF patients did not change significantly before and after food consumption (18). In the literature, there are studies showing that different diseases can be seen together with FMF in addition to autoimmune diseases. Tweezer-Zaks et al. conducted a study in which it was revealed that, cryptogenic cirrhosis was common in individuals with AAA than in the general population (19).

## Attacks and Affecting Factors in Patients with FMF

It is believed that environmental factors may play a role in the incidence of attacks in individuals with FMF and the severity of the disease. Also, there are different factors such as physical activity, menstruation, stress, fatigue, staying at 4 ° C 3 times a week and staying in the cold for more than 1 h, dietary patterns affect on the incidence of attacks (6,7,20). This may occur because of the effect of dietary fat and carbohydrates on inflammation (21). According to study conducted by Cebicci et al., there was no significant differences induced by a high-fat diet on the FMF triggers of attacks between female and male participants (6). Yenokyan and Armenian, in their study in 2012, revealed that high level of stress were associated with FMF attacks incidence. It was observed that diet high in fat did not increase the probability of FMF attacks. In this study, significantly higher rate of complete colchicine response was found in patients who preferred less salty or fatty foods (20).

A study conducted on individuals with FMF indicated that plasma IL-6 and TNF-α levels increased after consuming a diet that was rich in saturated fatty acids, and the same cytokines decreased after consuming a diet that was high in unsaturated fatty acids (22). Another study showed that a diet rich in fat, regardless of the type of fatty acid, increased IL-6 levels but had no effect on TNF-α levels (23). Kısla Ekinci et al., conducted study on 74 children with FMF, and reported that low-salt or low-fat diets could be helpful in changing the treatment of children with FMF (24). Although a wide variety of studies were published in the literature in recent years on FMF, the effect of dietary fat consumption in patients with FMF has not been examined, and the effect of salt consumption has not been

researched. First, in 1961, Mellinkoff et al. noted that a low-fat diet reduced the fever attacks in 8 patients with FMF (25). Then, Sohar et al. (1962) conducted a study on 32 FMF patients who did not take colchicine, of whom 8 could not comply with the diet due to their beliefs. It was stated in their study that colchicine was the gold standard of treatment and that a low-fat diet do not effect the period of FMF attacks. However, as the relationship between autoimmune diseases and gout has been clarified, dietary intake of A, D, E vitamins, phytoestrogens, and polyunsaturated fatty acids may have a positive effect on systemic lupus erythematosus, which is one of the autoimmune diseases (26). Furthermore, it has been concluded that high salt intake in the diet is effective in the transformation of T helper (Th) cells into proinflammatory Th17 subtypes (27). Studies have shown that salt intake causes epigenetic changes such as DNA demethylation in Th cells and ultimately leads to autoimmunity (28). Moreover high salt concentration causes proinflammatory cytokine production due to an overexpression of macrophages, dentritic cells, and overexpression of IL-13 (29).

Verrecchia et al. in a study conducted in 2017, reported that Helicobacter pylori infection can increase the frequency of FMF attacks, the growth of small intestinal bacteria, and a release of bacterial products and the effect. At the end of the study, it was concluded that the clinical results of patients improved with the treatment of intestinal bacterial growth (30).

## Some Nutrient Deficiencies in Patients with FMF

Some nutrient deficiencies in patients with FMF have been evaluated in some studies. In a study in which healthy children and children with FMF participated, the 25-hydroxyvitamin D levels of the participants were evaluated. As a result of the study, it was observed that the 25-hydroxyvitamin D levels of the children with FMF were significantly lower than in the control group. In this study where in the FMF diagnosis age of the participants was six, a significant difference was observed between age and the vitamin D levels (31). Lotfy et al., also aimed to assess the vitamin D level of in children with FMF in 2017. At the end of their study, like other studies' results, the vitamin D levels of the children with FMF were found to be lower than in the healthy controls. It was stated that this may have been caused by inflammation, and exhaustive studies are needed to evaluate the effect of taking pre and post vitamin D levels (32). In another study conducted on children with FMF, a significant correlation was found between the Pitssburg Sleep Quality Index (PSQI) and vitamin D levels. The total PSQI score was found to be significantly higher in individuals with vitamin D levels that were below 20 ng / mL in terms of sleep problems. In this study, vitamin D deficiency was observed in 36.5% of the individuals, while low vitamin D was found to be associated with poor sleep quality. Effective sleep was found to be significantly lower in participants with B12 levels that were below 200 pg / mL. At the end of the study, it was stated that B12 had a positive effect on the sleep quality in children with FMF (33). In a study conducted by Gemici et al., no deficiencies were observed in the B12 levels of FMF patients, who were undergoing colchicine treatment, but impairment tended to progress in some patients (34).

## Gut Microbiota Changes in Patients with FMF

Another investigated aspect of this issue is the effect of changes in gut microbiota in patients with FMF. Gut microbiota is affected by many factors, including hormonal changes, diet, lifestyle changes, some diseases, exposure to antimicrobial agents, ethnicity, etc. (35). Therefore, the mechanisms that change and regulate microbial patterns, such as diet, prebiotics, and antibiotics, on intestinal microbiota and host metabolism were aimed to be elucidated.

It is known that individuals with FMF, especially those with ethnic distribution, are sensitive to microbiota changes (35). Autoinflammatory genes such as MEFV in FMF or nucleotide-binding oligomerization domain-containing protein 2 (NOD2) /caspase recruitment domain-containing protein 15 (CARD15) in Chron's disease cause excessive response in the innate immune system (36). Both of these genes are localized on chromosome 16 (37). The MEFV and NOD2/CARD15 genes encode similar superfamily proteins and regulate cytokine processes, cell apoptosis, and inflammation (38). Chron's patients are carriers of mutated proteins and are more sensitive to bacterial products. It also stimulates innate immunity (39). NOD2/CARD15 mutations were not associated with increased susceptibility to FMF development.

However, in a study involving 103 children with FMF, a higher increase in colchicine resistance was found in individuals with NOD2 / CARD15 mutation, and the disease progressed more seriously than in individuals without the mutated gene (40). In a clinical study involving patients with FMF with mutations in the MEFV gene encoding pyrin, a congenital immunity-regulating protein, there were reduced total bacteria count, lower diversity, and changes in the bacterial populations in Bacteroidetes, Firmicutes, and Proteobacteria phyla (41). A series of 19 FMF patients who were examined while having an attack in the study identified a loss of diversity in the microbiata with changing in bacterial populations within the Firmicutes, Bacteroidetes, and Proteobacteria phyla when compared to the healthy controls. As a result, a lower proportion of Prevotellaceae, Dialister and Prevotella was found when compared to the controls. An increase was detected in the amount of Porphyromonadaceae, Phascolarctobacterium, Faecalibacterium and Parabacteroides. During remission, the amount of Ruminococcus, Enterobacteriaceae and Acidaminococcaceae was higher in the same subjects when compared to the controls, and the amount of Roseburia, which is a member of Firmicutes phylum, was found to be lower. It was concluded that host genes determine the host-microbiota interaction with an FMF-specific microbiota profile. In addition, an analysis of the mutations in the MEFV gene and gut showed that bacterial diversity, depletion of the total number of identified bacteria, loss of diversity, and large changes in the bacterial populations were dependent on the allelic carrier status of the host (41). AA Amyloidosis Study Group investigated the intestinal microbiota in patients with FMF in 2019. They were examined using 16S ribosomal RNA gene sequencing, and either had complications or did not develop any due to AA amyloidosis. As a result of the study, changes in the gut microbiota components were observed when compared to the healthy controls. An increase in the systemic concentrations of short and long-chain fatty acids produced by the gut microbiota was also

observed in the study, suggesting leaky gut syndrome. The leaky gut that can be seen in AAA and the passage of environmental components into the systemic circulation may exacerbate inflammation in AAA. It has been emphasized that gut microbiota has an important role in the pathogenesis of AA amyloidosis (42). The profile of microbial products and metabolites (especially the specific profile of long-chain fatty acids) in the human metabolome of FMF patients is thought to be a marker for disease (43). Similarly, blood short-chain fatty acid levels were found to be elevated in the acute period of the disease because of active inflammation (44). Lactobacillus acidophilus INMIA 9602 Er-2 strain 317/402, a probiotic strain isolated from the feces of a healthy newborn, produces a small anti-microbial peptide (bacteriocin acidosine LCHV) and shows broad activity against pathogens (44). The clinically proven positive effects of the strain have been confirmed in different studies, including in FMF patients (45). In the study, Lactobacillus acidophilus INMIA 9602 Er-2 strain 317/402 reduced only the Enterobacteriaceae, thus resulting in bacterial intestinal dysbiosis. In addition, the relative excess of Candida albicans, which is increased in FMF patients, was reduced.

Recently, a combination of 8 bacterial strains (Bifidobacterium breve DSM24732®, Streptococcus thermophilus DSM24731®, Bifidobacterium infantis DSM24737®, Bifidobacterium longum DSM24736®, Lactobacillus acidophilus DSM24735®, Lactobacillus acidophilus®, Lactobacillus acidophilus DSM24735) was tested. It was observed that this combination, given between attacks, may improve symptoms in a subset of FMF patients with more severe disease-associated MEFV variants and who are partially colchicine-resistant. However, there have been few well-designed, comprehensive, prospective studies on the effects of probiotics to prevent attacks in individuals with FMF, reduce symptoms, improve the efficacy of colchicine, and prevent complications (amyloidosis, etc.).

More studies are needed on the effect of specific probiotic treatments on symptoms and microbiota patterns without reducing the beneficial effects of the main treatment options in FMF patients (46).

## CONCLUSION

FMF is an autoinflammatory, autosomal recessive, rheumatic disease. FMF attacks occur at least 1-3 days on average in individuals, but there are different data on the frequency of attacks. There is limited literature knowledge related to whether food patterns may play a role in the incidence of FMF attacks or not. While current studies have focused on dietary patterns with high fat and high salt contents, it is known that individuals may also be exposed to a lack of different nutrients. Studies on the efficacy of some food supplements such as omega-3 and probiotics in anti-inflammatory diseases are needed in a disease such as FMF. The literature on this subject, and especially on foods that may affect the duration and frequency of attacks in individuals with FMF is lacking; thus, more clinical studies must be conducted. These should be aimed to increase the quality of life of individuals in this direction.

**Conflicts of Interest:**
The authors have no conflicts of interest to declare.

**Ethics Committee Approval:**
Ethics committee approval was not required.

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