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## Original Research

# Comparison of Vitamin D, B12, and Folic Acid Levels According to Attack Frequency in Familial Mediterranean Fever Cases

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### Abstract

**Objectives:** Familial Mediterranean fever (FMF) is an autoinflammatory disease more commonly observed in the Eastern Mediterranean region. Studies have shown that inflammatory processes may decrease vitamin D, vitamin B12 and folate levels, but there is no clear data on the effect of attack frequency on these levels. Our study aimed to evaluate the effect of FMF attack frequency on vitamin levels.

**Methods:** FMF patients aged between 4-18 years were considered as the study group, while healthy children who had vitamin levels during the same period were considered as the control group. The study group was further subgrouped according to the number of attacks. Those experiencing 2 or fewer attacks per year are classified as the attack group, while those experiencing 6 or more attacks per year are classified as the frequent attack group.

**Results:** A total of 494 subjects were included. The study group was composed of 333 FMF patients, 108 of them in the attack group and 225 in the frequent attack group. Control group included 161 children. The median and interquartile range (IQR: P25-75) in the frequent attack, attack, and control groups for 25(OH)D levels were 14.3 (9.57-18.9), 14.85 (10.12-21.77), and 14.95 (9.92-20.12) ng/ml, for B12 levels were 320 (238-415), 328 (250.25-439.25), and 373 (273.75-519.25) pg/ml, and for folate levels were 6 (5.13-8.12), 6.8 (5.36-8.9), and 7 (5.3-9.9) ng/ml, respectively. There is no significant difference between groups for 25(OH)D and folate ( $p=0.436$  and  $p=0.25$ , respectively). Vitamin B12 levels are significantly lower in study group ( $p=0.001$ ) but there is no difference according to attack frequency ( $p=0.92$ ).

**Conclusion:** There is no effect of attack frequency on 25(OH)D, vitamin B12 and folate levels. The fact that vitamin B12 levels are within normal limits in patients with FMF may be explained by the adequate dietary habits of these patients.

**Keywords:** Familial Mediterranean Fever, folate, vitamin B12, vitamin D

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Familial Mediterranean Fever (FMF) is an autosomal recessive inherited autoinflammatory disease characterized by recurrent fever and serositis. FMF is typically observed in populations of the Eastern Mediterranean (Armenian, Turkish, Arab, and non-Ashkenazi Jewish descent).<sup>[1]</sup> FMF attacks manifest with fever, chest pain, and joint pain and usually resolve within 24-72 hours. Rarely, attacks may persist for one week to one month. Patients are asymptomatic between attacks.<sup>[2]</sup> Studies have demonstrated that vitamin D has immunomodulatory properties that inhibit autoinflammatory processes via vitamin D receptors on T cells.<sup>[3]</sup> While studies have shown lower levels of 25-hydroxy vitamin D (25(OH)D) during attack periods in FMF cases, there is a lack of research investigating the impact of attack frequency on vitamin levels.<sup>[4]</sup> Additionally, publications are indicating that B12 vitamin and folate levels may be affected by inflammatory processes.<sup>[5,6]</sup> In this study, we aimed to determine whether vitamin deficiencies are more prevalent in FMF patients classified by attack frequency compared to healthy children by comparing the levels of 25(OH)D, B12 vitamin, and folate in FMF patients and healthy controls stratified by attack frequency.

## Methods

The study group consisted of patients aged 4-18 years diagnosed with FMF who presented to the Pediatric Nephrology Clinic between January 2022 and December 2022, and age- and gender-matched children without any additional diseases who presented to the Department of Pediatrics for routine check-ups during the same period were included as the control group. Patients who experienced fever, arthritis, chest pain, and abdominal pain during attacks were divided into two groups based on attack frequency: those experiencing two or fewer attacks per year were classified as the attack group, and those experiencing six or more attacks per year were classified as the frequent attack group. The 25(OH)D, B12, and folate levels and other parameters were evaluated in these patient groups. Serum vitamin lev-

els obtained during routine follow-up visits when patients were not in an attack period were included in the study. Patients diagnosed with FMF according to the criteria of Yalçinkaya et al.<sup>[7]</sup> and receiving colchicine treatment for at least 1 year were included in the study. Serum 25(OH)D levels <12 ng/ml were considered as vitamin D deficiency, while levels between 12-20 ng/ml were considered as vitamin D insufficiency.<sup>[8]</sup> Seasonal variations in 25(OH)D levels were disregarded in the study. Serum vitamin B12 levels <200 pg/dl and folate levels <3 ng/ml were considered deficient.<sup>[9]</sup> Before retrospective analysis of patient data, detailed information was provided to all patient guardians, and informed consent was obtained. The study was approved by the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital on 13.02.2024 (No: 4295) and conducted under the Helsinki Declaration.

## Statistical Analysis

Data were analyzed using IBM SPSS 22.0 (IBM Corporation 2011, NY) and TURCOSA. Categorical variables were summarized as values and percentages, while continuous variables were summarized as median and standard deviation. Mann-Whitney U test or Kruskal-Wallis test was used to compare continuous variables between groups for parameters that did not show normal distribution.

## Results

A total of 494 patients and healthy children were included in our study. A total of 333 FMF patients (188 Female/145 Male) who presented to our clinic in 2022 were included in the study. Among these patients, 108 were classified as having frequent attacks, while 225 were classified as having occasional attacks. The control group comprised 161 healthy children (87 Female/74 Male). The median and range values for age in the frequent attack, occasional attack, and control groups were 13 (4-18), 14 (4-18), and 12 (4-18), respectively ( $p=0.127$ ) (Table 1). Of the patients for whom genetic analysis was available, 9 were M694V/M694V homo-

**Table 1.** Demographic features of the study population

	Frequent Attack	Attack	Control	p
Age (Median/Range)*	13 (4-18)	14 (4-18)	12 (5-18)	$p=0.127^{**}$
Gender				
Female	64	124	87	$p=0.68^{**}$
Male	44	101	74	
MEFV Mutation Test Results				
M694V/M694V	9			
M694V/Other genotypes (R202Q, E148Q, V726A, M694I, M680I)	75			

\*\*Kruskal Wallis Test.

zygous, 75 were M694V/other genotypes (R202Q, E148Q, V726A, M694I, M680I), and 3 had a normal genotype. The median and interquartile range (IQR: P25-75) for 25(OH)D levels were 14.3 (9.57-18.9), 14.85 (10.12-21.77), and 14.95 (9.92-20.12) ng/ml in the frequent attack, occasional attack, and control groups, respectively, with no significant clinical or statistical differences observed between the groups ( $p=0.436$ ). Among the 494 children evaluated for 25(OH)D levels, vitamin D deficiency was detected in 62.8% and insufficiency in 17.8% (Table 2). When examined in the same order, the median and IQR: P25-75 for B12 levels were 320 (238-415), 328 (250.25-439.25), and 373 (273.75-519.25) pg/ml (Table 2). A statistically significant difference was observed between the FMF and control groups ( $p=0.001$ ), but no relationship was found between B12 levels and attack frequency ( $p=0.92$ ). Clinically significant B12 deficiency was observed in 9.3% of the 494 children evaluated for B12. The median and IQR: P25-75 for serum folate levels were 6 (5.13-8.12), 6.8 (5.36-8.9), and 7 (5.3-9.9) ng/ml, respectively, showing no variability ( $p=0.25$ ). Similarly, folate deficiency was observed in 1.8% of the 494 children evaluated for folate levels. When comparing vitamin levels based on attack frequency, no statistically or clinically significant differences were observed between the groups ( $p=0.19$  for 25(OH)D,  $p=0.92$  for B12,  $p=0.22$  for folate). The median 25(OH)D values according to gender were 12.6 ng/ml in females and 17.3 ng/ml in males, with significantly lower values observed in females ( $p<0.001$ ) in both the FMF and control groups.

## Discussion

In this study, no significant differences were observed in the levels of 25(OH)D, B12 vitamin, and folate according to attack frequency in FMF patients. However, a significant decrease in vitamin B12 levels compared to the control group was detected in FMF patients, while no significant differences were found between the groups in terms of vitamin D and folate levels. Studies have indicated that vitamin D has immunomodulatory effects by inhibiting increased proinflammatory cytokine release on T cells.<sup>[3,7]</sup> While literature

suggests a deficiency in 25(OH)D levels in FMF patients, there is insufficient information on how the frequency and severity of attacks are affected due to decreased immunomodulatory effects. Although studies comparing patients and healthy control groups have found lower 25(OH)D levels in FMF patients, our study did not find a significant difference. Low vitamin D levels in FMF patients may be due to lack of physical activity capacity and limited exposure to sunlight and Decreased appetite and malnutrition due to chronic disease and inflammation may also contribute. However, a high prevalence of vitamin D deficiency in the healthy controls was also found (33% and 25% in patients and healthy controls, respectively). Our study did not include factors that may affect vitamin D levels such as daily physical activity capacity, duration of exposure to sunlight, clothing style and eating habits. Due to these factors affecting vitamin D levels, there may not have been a significant difference between the healthy control group and patients with FMF.<sup>[4]</sup>

B12 levels were significantly lower in FMF patients compared to the control group in our study but B12 levels were normal in all groups. All FMF patients in our study were receiving regular colchicine treatment, and the decrease in B12 levels in these cases may be due to colchicine-induced intestinal malabsorption.<sup>[10,11]</sup> Additionally, although few studies have reported on the relationship between B12 vitamin and inflammatory processes, it has been suggested that B12 levels decrease during inflammatory processes.<sup>[6]</sup> Gemici et al.<sup>[12]</sup> demonstrated a fourfold higher incidence of B12 deficiency in FMF patients compared to the control group. Yesilova et al.<sup>[13]</sup> reported lower B12 and folate levels in patients with Behçet's disease compared to the control group in a study published in 2005, suggesting that this condition may be associated with increased catabolism or utilization of vitamins due to chronic inflammation. Although our study did not support the hypothesis of B12 malabsorption due to colchicine use in patients with FMF, it was found to be at a lower level compared to healthy children. In addition, the B12 level was not affected by the frequency of attacks in patients with FMF.

**Table 2.** Vitamin level comparison between frequent attack, attack and control group

Variables	Frequent attack (n=108)	Attack (n=225)	Control (n=161)	p
Vitamin levels (Median/IQR: P25-75)				
25(OH) Vitamin-D (ng/ml)	14.3 (9.57-18.9)	14.85 (10.12-21.77)	14.95 (9.92-20.12)	$p=0.436^*$
Vitamin B12 (pg/ml)	320 (238-415)	328 (250.25-439.25)	373 (273.75-519.25)	$p=0.001^*$
Folic acid (pg/ml)	6 (5.13-8.12)	6.8 (5.36-8.9)	7 (5.3-9.9)	$p=0.25^*$

\*Mann Whitney U test and Kruskal-Wallis test.

While there are studies evaluating the association of folate levels with systemic inflammatory processes, there is no clear evidence in the literature indicating a decrease in folate levels due to inflammatory processes. Karatay et al.<sup>[14]</sup> did not report any difference in serum folate levels between FMF patients and the control group in a study published in 2010.

## Conclusion

25(OH)D deficiency and insufficiency affect children worldwide. Healthy children also have a high prevalence of vitamin D deficiency and insufficiency. The serum 25(OH)D levels were found to be similar in FMF compared to healthy children. 25(OH)D, vitamin B12 and folate levels were not affected by the frequency of attacks. We believe that further studies in larger series will focus on the relationship of 25(OH)D, vitamin B12 and folate levels with the frequency of attacks and their role in autoinflammatory processes.

## Disclosures

**Patient Informed Consent:** Before retrospective analysis of patient data, detailed information was provided to all patient guardians, and informed consent was obtained.

**Ethics Committee Approval:** The study was approved by the Ethics Committee of Sisli Hamidiye Etfal Training and Research Hospital (Date: 13.02.2024, No: 4295).

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