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SHORT COMMUNICATION

Decreased vitamin D levels in patients with familial mediterranean fever

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Abstract Familial mediterranean fever (FMF) is an autosomal recessive disorder caused by mutations in the FMF gene (MEFV). The gene causing FMF, designated MEFV, encodes a protein called pyrin or marenostrin that is expressed mainly in myeloid bone marrow precursors, neutrophils, and monocytes. Since there are several etiological factors, FMF is the most common periodic fever syndrome. However, it is still unknown what triggers or ends these periodical attacks. As a pleiotropic hormone, vitamin D has immunomodulation effects. The aim of this study was to evaluate the vitamin D levels in FMF patients. The study group was comprised of 26 patients diagnosed with FMF (men/women: 12/14), and 34 healthy control (men/women: 17/17). Vitamin D levels in FMF patients and healthy controls were 11.05 ± 7.11, 17.15 ± 6.49, respectively. FMF patients had significantly decreased vitamin D levels compared with healthy controls ($P < 0.001$). In conclusion, it is thought that vitamin D deficiency in FMF patients may trigger the attacks. Further studies with larger patient populations need to hold to investigate the vitamin D deficiency in patients with FMF and that may assist to clarify the mechanism behind the colchicines resistant cases.

Keywords Familial mediterranean fever · Vitamin D · T cell

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Introduction

Familial mediterranean fever (FMF) is an autosomal recessive disease which predominantly affects certain ethnic groups, mainly Sephardic Jews, Turks, Arabs, and Armenians [1]. The gene causing FMF, designated MEFV, encodes a protein called pyrin or marenostrin that is expressed mainly in myeloid bone marrow precursors, neutrophils, and monocytes [2]. Since there are several etiological factors, FMF is the most common periodic fever syndrome. However, it is still unknown what triggers or ends these periodical attacks. The most common clinical manifestations are serositis (peritonitis, pleuritis, and pericarditis), arthritis, and pleurisy accompanied by fever. Despite colchicines is the only effective treatment, up to 30% of the FMF patients those who are resistant to colchicines are still a problem.

Vitamin D is a steroid hormone which is essentially needed in the homeostasis of calcium and phosphorus and for the functioning of musculoskeletal system. Vitamin D has immunomodulation and pleiotropic effects. Supplementation of vitamin D was shown to be therapeutically effective in various animal models such as systemic lupus erythematosus, inflammatory bowel disease, and collagen-induced arthritis [3–5].

Circulating levels of vitamin D have been shown to decrease in several inflammatory conditions including rheumatoid arthritis, systemic lupus erythematosus and

Behcet's disease [6–8]. However, to the best of our knowledge, up to date the role of the vitamin D in FMF has not been assessed. The aim of this study is to investigate vitamin D levels in FMF patients.

Materials and methods

The study population divided into two groups, while the first group composed of 26 FMF patients (men/women: 12/14), second group was including 34 healthy control (men/women: 17/17). The diagnosis of FMF was established in accordance with the Tel-Hashomer criteria [9]. All FMF patients were in attack-free period. Mean duration of the disease was 154.34 ± 47.26. The FMF attacks were recorded according to the patients' reports. The mean frequency of the attacks for 6 months with FMF patients were 2.61 ± 2.53. There were three colchicine-resistant patients whose vitamin D levels were significantly decreased. None of the cases had dermatologic finding or amyloidal accumulation. All FMF patients were receiving 1–1.5 mg/day of colchicines therapy, and none of the patients were receiving any drug other than colchicines that could influence vitamin D levels. Healthy controls and FMF patients had neither bone diseases nor using drugs that could effect bone metabolism, and the blood samples were obtained in the same season from all of the subjects to avoid the seasonal variation of the sun on vitamin D. 25 (OH) D was used to determine vitamin D level. All participants were informed about the study, and the procedures were in accordance with Declaration of Helsinki and institutional guidelines. The study was approved by the Gaziantep University medical faculty ethics committee.

Statistical analysis: nonparametric Mann–Whitney *U* test and paired *t* test were used to analyze the data. A *P* value <0.05 was considered statistically significant.

Results

The mean age of FMF patients and healthy control were 32 ± 13.3, and 34.74 ± 11.9 years, respectively. Demographic features and vitamin levels are demonstrated in Table 1. Concerning the demographic features, the groups were with similar age and gender (for each, $P > 0.05$). Vitamin D levels in FMF patients and healthy controls were 11.05 ± 7.11 and 17.15 ± 6.49, respectively. Vitamin D levels were remarkably decreased in patients with FMF in contrast to healthy controls ($P < 0.001$) (Fig. 1).

Table 1 Demographic features and vitamin levels of study groups

	FMF patients ($n = 26$)	Healthy control ($n = 34$)	*P*
Age (years)	32 ± 13.3	34.74 ± 11.9	>0.05
Sex (male/female)	12/14	17/17	>0.05
25 (OH) D (ng/mL)	11.05 ± 7.11	17.15 ± 6.49	<0.001

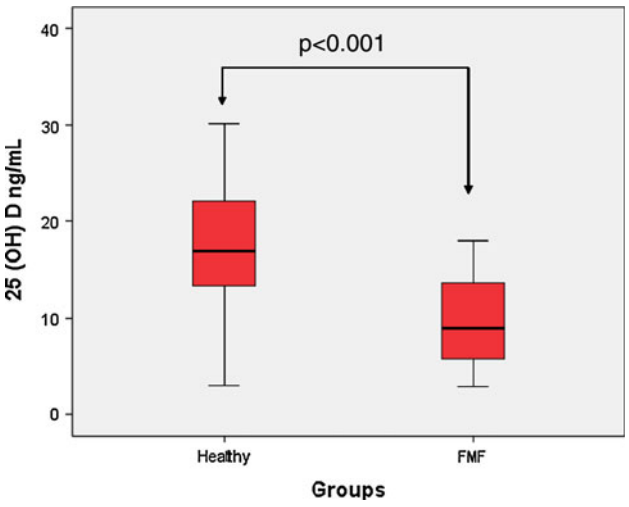


Fig. 1 Vitamin D levels in study groups

Discussion

This study attempts to demonstrate that vitamin D levels were remarkably decreased in patients with FMF in contrast to healthy controls. To the best of our knowledge, this is the first study that investigates vitamin D levels in patients with FMF.

The immune system is regulated by T-helper cells (Th) which develop different immune responses. T-helper cells consist of type 1 Th-cells (Th1) and type 2 Th-cells (Th2). The primary cytokines produced by human Th1 cells are interferon (IFN)-γ and tumor necrosis factor (TNF)-β, whereas Th2 cells produce interleukins IL-4 and IL-5 [10, 11]. FMF shows a Th1 polarization and that leads to inflammation. Köklü et al. [12] found increased plasma IFN-γ levels in FMF patients both with and without attack as compared to healthy controls. Aypar et al. reported that IFN-γ were higher during acute attacks compared with attack-free periods with FMF patients. IL-4, which is a Th2 type cytokine, was not significantly different during attacks and attack-free period [13].

Low level of vitamin D level was associated with many autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes. It was demonstrated that vitamin D has crucial role in proliferation, differentiation, and maturation of the different cells of immune system such as dendritic cells, macrophages, monocytes, and lymphocytes [14–16]. Vitamin D has been

found to play vital role in T lymphocyte proliferation, especially in the Th1 arm [17]. On the other hand, the effect of vitamin D on the Th2 cell is controversial. IL-4 has been increased by the treatment of vitamin D, but staeva-Vieira et al. shown that IL-4 has been inhibited [18, 19]. In the light of these findings, it can be said that deficiency of vitamin D in patients with FMF might have activated the inflammatory cytokine network. Despite the presence of some common reasons like physical exertion, emotional stresses, and menses associated with attacks, the exact mechanism triggering the FMF attacks are unclear. We thought that vitamin D deficiency could explain the mechanism that triggers the FMF attacks.

While our study population was limited and there were only two patients whom had resistant FMF diagnosis, we did not evaluate the prognosis after vitamin D replacement. The absence of a diseased control group could be our second limitation to compare vitamin D levels in FMF with other rheumatic diseases, such as ankylosing spondylitis, rheumatoid arthritis, etc.

Consequently, the deficiency of vitamin D in FMF patients could trigger the attacks. Further studies with larger patient groups need to be held, especially with those who have colchicines resistant to explain the mechanism behind FMF attacks.

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