Original Investigation / Özgün Araştırma

Impact of Vitamin D Deficiency on Disease Severity and Quality of Life in the Patients with Familial Mediterranean Fever

Ailesel Akdeniz Ateşi Hastalarında D Vitamini Eksikliğinin Hastalık Şiddeti ve Yaşam Kalitesi Üzerine Etkisi

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ABSTRACT

Objective: Low vitamin D status is increasingly thought to be associated with inflammatory rheumatic diseases. In our study, we aimed to investigate vitamin D deficiency in patients with familial Mediterranean fever (FMF), and evaluate its impact on disease severity and health-related quality of life (HRQoL).

Methods: Sixty-five FMF patients were included in the study. Serum 25-hydroxy-vitamin D levels were measured using a radioimmunoassay kit technique using isotech 20 gamma counter device (STRATEC SR-300, Birkenfeld, Germany). Patients were divided into two groups according to level of vitamin D. Group 1 involved 33 patients with low vitamin D level (< 20 ng/ml), and group 2 involved 32 patients with vitamin D level in normal ranges (≥20 ng/ml). HRQoL was evaluated by Short Form-36 (SF36), disease severity by Disease Severity Score developed by Mor, and pain by Visual Analog Scale-pain (VAS-pain).

Results: Moderate and high disease severity scores were mostly found in group 1, whereas low disease severity scores were found in group 2. Group 1 had higher FMF disease severity than group 2 (Pearson X2=21.504, p<0.001). Pain severity was significantly higher in group 1 (p=0.024). Patients in group 1 scored significantly higher in general health subgroup of SF36 (p=0.016).

Conclusion: Vitamin D deficiency is common in FMF and associated with higher disease severity, pain and deterioration in quality of life. In FMF patients, it will be an appropriate approach to evaluate vitamin D status and correct its deficiency.

Keywords: Familial Mediterranean fever, pain, quality of life, vitamin D deficiency

ÖZET

Amaç: Düşük D vitamin düzeyinin inflamatuar romatizmal hastalıklarla ilişkili olduğu gittikçe daha fazla düşünülmektedir. Çalışmamızda ailevi Akdeniz ateşi [familial Mediterranean fever (FMF)] hastalarında vitamin D eksikliğini araştırmayı ve bunun hastalık şiddeti ve sağlıkla ilişkili yaşam kalitesi [health-related quality of life (HRQoL)] üzerine etkisini değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya altmış beş FMF hastası dahil edildi. Serum 25-hidroksi vitamin D seviyeleri radioimmunoassay kit tekniği ile izotech 20 gama sayacı cihazı ile (STRATEC SR-300, Birkenfeld, Germany) ölçüldü. Hastalar vitamin D düzeyine göre iki gruba ayrıldı. Grup 1 düşük D vitamini olan (< 20 ng/ml) 33 hastayı ve grup 2 ise normal sınırlarda D vitamini düzeyine sahip (≥20 ng/ml) 32 hastayı içerdi. HRQoL, kısa form-36 [Short Form-36 (SF36)]; hastalık şiddeti Mor tarafından geliştirilmiş olan Hastalık Şiddet Skoru; ağrı ise Görsel Analog Skala-ağrı Visual Analog Scale-pain (VAS-pain) ile değerlendirildi.

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Bulgular: Orta ve yüksek hastalık şiddet skorları grup 1'de, düşük hastalık şiddet skorları ise grup 2'de daha fazla bulundu. Grup 1, grup 2'ye göre daha yüksek FMF hastalık şiddetine sahipti (Pearson X2=21.504, p<0.001). Ağrı şiddeti belirgin olarak grup 1'de daha yüksekti (p=0.024). Grup 1'deki hastalar SF36 genel sağlık alt grubunda anlamlı olarak daha yüksek skor kaydetti (p=0.016).

Sonuçlar: Vitamin D eksikliği FMF'de sıktır ve daha yüksek hastalık şiddeti, ağrı ve yaşam kalitesinde bozulma ile ilişkilidir. FMF hastalarında vitamin D düzeyini değerlendirmek ve eksikliği düzeltmek uygun bir yaklaşım olacaktır.

Anahtar sözcükler: Ailesel Akdeniz ateşi, ağrı, yaşam kalitesi, vitamin D eksikliği

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease, which is prevalent among people of Mediterranean descent, but may affect any ethnic group (1). It is currently regarded as a member of the hereditary periodic fever syndromes, and a subset of the autoinflammatory diseases (2). FMF is characterized by recurrent febrile inflammatory attacks of serosal and synovial membranes (3). The etiology and pathogenesis of FMF is not clearly known. Immune mechanisms play a major role in FMF (4).

Vitamin D is mainly known for its favorable effects in calcium and bone metabolism. Beyond its functions in calcium homeostasis, vitamin D plays an essential role in the immunomodulation (5,6). Immunomodulation is mediated through the vitamin D receptor (VDR). VDR activation in immune cells leads to the transcription of gene products that trigger a cascade of antiproliferative and immune regulatory processes (7).

Vitamin D deficiency, defined mostly as serum 25-hydroxyvitamin D levels of <20 ng/ml (8), is increasingly thought to be associated with various rheumatic diseases such as rheumatoid arthritis, spondyloarthropathies, Behcet's disease, polimyositis/dermatomyositis, systemic lupus erythematosus and systemic sclerosis (9, 10, 11). Moreover, in previous studies, vitamin D deficiency has been found to be correlated with disease severity and activity in autoinflammatory diseases including rheumatoid arthritis and systemic lupus erythematosus (12, 13).

Vitamin D deficiency in FMF has been recently mentioned in the literature (14, 15, 16, 17). The main objectives of the present study are i) to investigate vitamin D deficiency in the patients with FMF; ii) to evaluate the association between vitamin D deficiency and disease parameters including disease severity and pain, and iii) to determine the impact of vitamin D deficiency on health-related quality of life (HRQoL).

Materials and Methods

A total of 65 FMF patients (aged 18-80) who were admitted to outpatient physical medicine and rehabilitation, and rheumatology clinics of Kocaeli Training and Research Hospital between May and September 2014 were consecutively enrolled. All of the patients fulfilled the criteria by Livneh et al. (18) for the diagnosis of FMF. None of the patients were in attack period. All of the patients were under regular colchicine (0.5-1.5 mg/day) therapy. Exclusion criteria were concomitant rheumatic diseases such as inflammatory bowel disease, Behcet's disease and ankylosing spondylitis, chronic diseases such as liver and kidney insufficiency which may affect vitamin D metabolism and use of any medication which may affect the serum vitamin D level. Serum vitamin D levels were measured using a radioimmunoassay kit technique using isotech 20 gamma counter device (STRATEC SR-300, Birkenfeld, Germany). Vitamin D levels less than 20 ng/ml were considered as deficient (8). The patients were divided into two groups according to the level of vitamin D: group 1 consisted of 33 patients with low vitamin D level (< 20 ng/ml), and group 2 consisted of 32 patients with vitamin D level in normal ranges (≥20 ng/ml). Erythrocyte sedimentation rate (ESR) was measured by Westergren tube method (LENA infrared LED optical system, Montgat, Spain) and C-reactive protein (CRP) was measured by nephelometric method (Beckman Coulter, Brea, CA, USA). HRQoL was evaluated by using Short Form-36 (SF36) (19), and disease severity by Disease Severity Score developed by Mor (20).100 mm Visual Analog Scale-pain (VAS-pain) was used for measuring severity of pain (21).

Written informed consent was obtained from all of the patients. The study protocol was approved by the Medical Research Ethics Committee of training and research hospital. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Statistical Analyses

Descriptive statistics [mean, median, SD (Standard deviation), minimum, maximum and frequencies] were used for assessing the demographics and clinical parameters. Differences among groups were assessed using independent samples T-test. Chi-square test was used for categorical variables. The presence of correlation was evaluated by Spearman's correlation coefficients. A value of p<0.05 was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0 (Armonk, New York, USA).

Results

Demographic and Clinical Characteristics and Laboratory Parameters of the Patients

Sixty-five patients with FMF (35 women and 30 men) participated in this study. Group 1 consisted of 33 patients (20 women and 13 men), and group 2 consisted of 32 patients (15 women and 17 men). Mean age was 32.72±9.59 in group 1 and 34.63±9.73 in group 2. Age and gender did not significantly differ among the groups (p=0.43 and 0.27, respectively). Of all of the patients, mean disease duration was 15.18±12.16 (1-50) years, age of onset was 17.98±12.54 (3-44) years, age of diagnosis was 27.03±11.98 (3-51), and duration of attacks was 2.55±0.77 (1-7) days. Mean VAS-pain was 55.2±25.82 (20-100). Mean ESR was 17.63±11.05 (4-52) mm/hr [Normal range 0-20 mm/hr] and CRP was 7.73±11.29 (1.3-20) mg/dl [Normal range 0-4.99 mg/dl]. Of the patients, 30.8% (20 patients) had low, 53.8% (35 patients) had moderate, and 15.4% (10 patients) had high disease severity, according to Disease Severity Score developed by Mor. Fifteen patients (23.08%) had homozygote mutation for M694V, 19 patients (29.23%) had heterozygote mutation for M694V, 17 patients (26.15%) had other genetic mutation. 14 patients (21.54%) had no MEFV mutation.

Demographic and clinical data were given in Table 1.

Comparison of the Groups in Terms of Disease Parameters and Health-Related Quality of Life

Mean vitamin D level of all of the patients was 19.02±11.45 ng/ml (4-55). Vitamin D deficiency was found in 33 patients (50.8%). The mean vitamin D level was 10.15±5.37 in these 33 patients (group 1), and 28.17±8.41 in remaining 32 patients (group 2). Vitamin D level was significantly lower in group 1 (p<0.001). Mean VAS-pain was 62.27±25.53 in group 1, and 47.91±24.39 in group 2. Severity of pain was significantly higher in group 1 (p=0.024). Patients in group 1 scored significantly higher in general health subgroup of SF36 (p=0.016) (Table 2).

Spearman's rank correlation test revealed that increase in ESR and CRP levels was not correlated with decrease in vitamin D levels (p=0.19, r=0.16 and p=0.94, r=-0.009, respectively).

Table 1. Clinical characteristics of FMF patients.

Parameters		Mean±SD (range) / n (%)
Age		33.66±9.64 (18-50)
Vitamin D (ng/ml)		19.02±11.45 (4-55)
BMI (kg/m^2)		25.67±3.94 (19-37)
ESR (mm/hr)		17.63±11.05 (4-52)
CRP (mg/dl)		7.73±11.29 (1.3-20)
VAS-pain		55.2±25.82 (20-100)
Disease duration (year)		15.18±12.16 (1-50)
Age of onset (year)		17.98±12.54 (3-44)
Age of diagnosis (year)		27.03±11.98 (3-51)
Number of attacks	≥2 attacks / month	3(4.62)
	2 attacks / month-1 attack / 6 months	30(46.15)
	≤1 attack / 6 months	32(49.23)
Duration of attacks (day)		2.55±0.77 (1-7)
Disease severity score	Mild	20 (30.8)
	Moderate	35 (53.8)
	Severe	10 (15.4)
Gene mutation	M694V/M694V	15(23.08)
	M694V/other	19(29.23)
	Other/other	17(26.15)
	No mutation	14(21.54)

FMF: *Familial Mediterranean fever,* ***BMI:*** *Body mass index,* ***ESR:*** *Erythrocyte sedimentation rate,* ***CRP:*** *C-reactive protein,* ***VAS:*** *Visual analog scale*

Table 2. The comparison of VAS-pain and SF36 subgroups.

	Group 1 (n=33) mean±SD	Group 2 (n=32) mean±SD	p value
VAS-pain	62.27±25.53	47.91±24.39	0.024*
SF36-physical function	68.03±23.08	72.19±26.49	0.502
SF36-physical role	41.67±44.05	55.47±41.99	0.201
SF36-bodily pain	53.18±25.94	65.63±24.73	0.052
SF36-general health	44.03±27.33	59.06±21.25	0.016*
SF36-vitality	47.87±24.75	58.19±20.01	0.07
SF36-social functioning	59.83±20.43	67.51±22.88	0.158
SF36-emotional role	51.52±40.91	60.41±40.11	0.38
SF36-mental	59.03±13.79	58.00±13.93	0.77

VAS: *Visual analog scale,* ***SD:*** *Standard deviation,* ***SF36:*** *Short form-36,* ****:*** *p <0.05 (significant)*

Moderate and high disease severity scores were most frequently found in group 1, whereas mild disease severity scores were found in group 2. When groups were compared in terms of disease severity scores, group 1 had higher disease activity levels than group 2. (Pearson X^2=21.504, p<0.001) (Table 3).

Table 3. The relation between vitamin D deficiency and disease activity.

		Vitamin D deficiency		p value
		present n(%)	absent n(%)	
Disease activity	mild	2 (6.06)	18(56.25)	<0.001**
	moderate	22(66.67)	13 (40.63)	
	severe	9(27.27)	1 (3.13)	

Pearson chi-square=21.504, *****:*** *p <0.01 (highly significant)*

Discussion

Vitamin D deficiency is a major health problem in the world. Recent epidemiologic surveys of the general population have suggested that the prevalence of vitamin D deficiency in developing countries is between 30- 90% (22). The rate of vitamin D deficiency varies greatly within countries and regions. It was reported as 8% in Estonia (23), 17.8% in Italy (24), 26-28% in Finland (25), and 74.9% in Aegean region of Turkey (26) in winter.

Vitamin D has been found to have immunomodulatory effects (27). Active vitamin D or 25 (OH) D3 has crucial role in proliferation, differentiation and maturation of the different immune system cells including dendritic cells, macrophages, monocytes, and lymphocytes (15). It inhibits T lymphocyte proliferation, and the expression of interleukin-2 (IL-2) and interferon-γ (IFN-γ) [28]. It induces expression of IL-10 and transforming growth factor (TGF)-β (7). In addition to its inhibitory effects on T lymphocytes, it reduces B lymphocyte proliferation, plasma cell differentiation and inhibits immunoglobulin release (10). Vitamin D deficiency has been found to be linked with autoimmune diseases such as diabetes mellitus (29), rheumatoid arthritis (30), Behcet's disease (31), systemic lupus erythematosus (32), multiple sclerosis (33), and inflammatory bowel disease (34). Moreover, several studies have confirmed a relationship between low vitamin D status and high disease activity in autoimmune inflammatory diseases. Ben-Zvi (35) and Toloza (36) have reported an association between low vitamin D status and high disease activity in the patients with systemic lupus erythematosus.

FMF is the most common autoinflammatory disease of unknown etiology. It is caused by mutations in MEFV (MEditerranean FeVer) gene, located on the short arm of chromosome 16, which encodes a 781 amino acid protein termed pyrin or marenostrin (37). The mutations of the MEFV gene are associated with an increase in IL-1β and tumor necrosis factor (TNF)-α production and an enhanced immune system response (14).

Vitamin D deficiency in FMF patients has been previously reported in the literature. In a study of Kisacik et al. (15), conducted in Turkish patients with FMF, it was found that FMF patients had significantly decreased vitamin D levels compared with healthy controls. They reported that vitamin D deficiency might trigger FMF attacks. Similarly, Erten et al. (14) found that vitamin D deficiency was more frequent in the patients with FMF than healthy controls. On the other hand, Anik et al. (17) investigated vitamin D deficiency in the children with FMF and suggested that serum vitamin D levels of FMF patients were significantly lower than healthy controls. Also Yilmaz et al. (16) reported decreased vitamin D levels in the children with FMF.

To our knowledge, our study is the first to demonstrate the association between vitamin D deficiency and disease severity in the adult patients with FMF. We evaluated disease severity by using Disease Severity Score developed by Mor. We found a positive relation between FMF disease severity and vitamin D deficiency. Previously, Yilmaz et al. (16) evaluated the relationship between vitamin D deficiency and disease severity, which was measured by using Pras disease severity score, in the children with FMF. They found no association. We also investigated the relationship between decrease in vitamin D levels and increase in inflammatory markers including ESR and CRP and found no correlation. In contrast, Erten et al. (14) found that increase in CRP, ESR and fibrinogen levels was significantly correlated with decrease in vitamin D levels. Similar to ours, their patients were not in attack period.

Our results also revealed a correlation between vitamin D deficiency and severity of pain. Similar relationships between vitamin D deficiency and pain intensity were previously reported in rheumatoid arthritis, another autoinflammatory disease (38, 39).

HRQoL is defined as "individuals' perceptions of their conditions in life, with regard to their objectives, expectations, norms and concerns, within the context of their own cultural and value systems " (40). Rheumatic disorders are among the main conditions, in which HRQoL is decreased (41). Previous studies have demonstrated poor HRQoL scores in the patients with FMF (42, 43). To the best of our knowledge, this is the first study which examined the effect of vitamin D deficiency on HRQoL in FMF patients. Our study showed that vitamin D deficiency had a negative impact on HRQoL in terms of general health, however we did not find an association between vitamin D deficiency and HRQoL including physical, emotional and social functions.

Mean vitamin D level of our patients was 19.02 ng/ml, indicating vitamin D deficiency. Our results were in accordance with previous studies. Kisacik (15) found this level as 11.05 ng/ml, Anik (17) as 12.9 ng/ml, Erten (14) as 9.2 ng/ml, and Yilmaz (16) as 15.94 ng/ml.

Our study has some limitations. First one is relatively small number of subjects. And second one is the lack of information on dietary vitamin D intake, sunlight exposure, and clothing styles of FMF patients, thus impact of these factors on serum vitamin D levels could not be assessed.

In conclusion, we have shown that vitamin D deficiency is associated with higher disease severity and pain in the patients with FMF. It has a negative effect on HRQoL. In FMF patients, it is convenient to evaluate and correct low vitamin D status. Further studies are needed to determine the effect of vitamin D supplementation on clinical status of FMF.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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