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Vitamin D Levels in Patients with Familial Mediterranean Fever During Attacks and Attack-Free Periods

Aykac Cebicci Mehtap[1], MD,

Cebicci Huseyin[2], MD

[1] Department of Physical Therapy and Rehabilitation, Kayseri City Hospital, Kayseri, TURKEY

[2] Department of Emergency Medicine, Kayseri City Hospital, Kayseri, Turkey

Abstract

Objective: In the present study, we aimed to investigate vitamin D levels among Familial Mediterranean Fever (FMF) patients both during attacks and attack-free periods and evaluate its association with attacks.

Material and Method: Twenty patients in the attack and twenty patients in the attack-free period were enrolled in the study. 25 hydroxyvitamin D levels were quantified using a high performance liquid chromatography (HPLC) method. Patients were questioned for their complaints during an attack, medications they were using, the frequency of attacks, their family history and duration of disease.

Results: %72,5 of all patients had 25 hydroxyvitamin D deficiency.25 hydroxyvitamin D level (mean ± SD) was 17.9 ± 7.8 ng/ml for patients in the attack period and 14.1 ± 7.13ng/ml for patients in the attack-free period. There was no statistically significant difference between the 2 groups in vitamin D levels (p=0,1). We did not find a significant association between attack frequency and vitamin Dlevels. (r=0,27 p=0.09). However there was a statistically significiant difference between genders in vitamin D levels and attack frequency. (p=0.04; p=0.01)

Conclusions: In this study there was no significant association between attack frequency and vitamin D levels, however there was a significantly difference in attack frequency between genders. Future studies with a larger number of patients would be beneficial in evaluating the relationship between vitamin D levels, genders and attack frequency in FMF patients.

Keywords: Familial Mediterranean Fever, attacks, vitamin D, 25(OH) D, genders

Introduction

Familial Mediterranean Fever (FMF) is an auto somal recessive disorder characterized by recurrent acute fever episodes and inflammation of serous membranes (Topaloglu at al., 2010, BerkunandEisenstein,2014 and On en, 2006). Familial Mediterranean Fever is caused by mutations in the MEFV gene which is located in the short arm of chromosome 16.MEFV gene encodes a protein called pyrin which prevents migration of leukocytes into serous membranes by

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suppressing the production of interleukin 1 beta(IL-1β). This suppressive mechanism is abolished as a result of mutations in the MEFV gene and thus, proinflammatory reactions remain chronically active (Onen,2006, Cakmak et al., 2013, Erten et al., 2013 and Rimar et al., 2012).

The most common symptoms experienced by FMF patients during attacks are fever and peritonitis (BerkunandEisenstein,2014 and Erten et al., 2013). Abdominal pain is the predominant clinical manifestation and occurs in 95% of all patients (On en, 2006 and Eaten et al., 2013). Other symptoms seen during an attack include arthritis, arthralgia, chest pain and erysipeloid skin lesions (Topaloglu at al., 2010 and Rimar et al., 2012). Attacks are irregular, usually lasting less than 3 days. Between the attacks patients are asymptomatic (Topaloglu at al., 2010, BerkunandEisenstein,2014 and Onen, 2006). Emotional stress, viral infections, trauma, physical activity and menstruation have been cited as external factors that trigger the attacks in FMF patients but it is still not clear what initiates inflammation and attacks (Topaloglu at al., 2010 and Karadag et al., 2013).

Vitamin D is a steroid hormone which has an important role in bone metabolism and it also shows immunomodulatory effects. Vitamin D is primarily involved in the regulation and differentiation of immune cells including lymphocytes, macrophages and natural killer cells. Vitamin D deficiency plays a role in the development of immune system-mediated disorders (Marques et al., 2010). Several studies have reported an association between Vitamin D deficiency and autoimmune diseases including romatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and multiple sclerosis (Karadag et al., 2013, Marques et al., 2010 and Kisacik et al., 2013).

Few studies exist in literature on vitamin D status in FMF patients which assessed vitamin D levels during attack-free period in FMF patients and found low vitamin D levels (Erten et al., 2013, Kisacik et al., 2013 and Anık et al., 2014). We designed the present study to investigate vitamin D levels in FMF patients both during attacks and attack-free periods and to determine whether there is an association between vitamin D levels and attacks.

Material and Methods

The study included 20 patients with diagnosis of FMF who admitted to the Emergency Department of Kayseri Research and Training Hospital with an acute attack and 20 patients with diagnosis of FMF in the attack-free period who were being followed at the Physical Therapy and Rehabilitation Outpatient Clinic. Those patients who presented with manifestations of fever and/or peritonitis, pleuritis, arthritis and prolonged febrilemyalgia who had formerly exhibited similar clinical pictures, patients who admitted with clinical symptoms within the first 72 hours of an attack and patients who had a body temperature over 37.5°C without any identified source of fever were considered to be in the attack period. Those patients who did not experience an attack for at least 3 weeks were considered to be in the attack-free period.

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Patients who had amyloidosis, a history of vitamin D use within the last 6 months and disorders affecting bone metabolism such as hyperthyroidism and hyperparathyroidism were excluded from the study.

Patients were questioned for their complaints during an attack, medications they were using, the frequency of attacks, their family history and duration of disease.25 hydroxyvitamin D(25 (OH)D)levels were measured by an Aligent (Germany) 1200 series device using HPLC methodology(high performance liquid chromatography) and concentrations less than 20ng/ml were considered as deficient levels. All of patients (with or without current attack) were enrolled the study in the same reason to avoid the seasonal variation of the sun on vitamin D. In attack period blood samples were taken in Emergency Department. Based on the attacks that patients experienced within the last 6 months, the attack frequency was categorized as once weekly, once in every 15 days, once in a month and once in more than a month. Ethics committee approval was obtained for the study and patients gave informed consent.

Data were entered into the SPSS statistics software. Values are provided as mean ±standard deviation (x±sd), median(min-max) and percent. Kolmogorov-Smirnov test was used to determine whether the data conformed to normal distribution. For between-group comparisons, chi-square test was used for qualitative data and independent- t test for quantitative data. Associations between data were evaluated using Spearman's correlation analysis. P value below 0.05 was considered statistically significant.

Results

A total of 40 patients were enrolled in the study including 20 in attack period and 20 in attack-free period. The mean age of patients was 33.7±12.7 years and mean duration of disease was 5.5±3.9 years. 72.5% of all patients were found to have 25(OH) D deficiency. Of patients who were in the attack period, 11 had symptoms of fever and abdominal pain and3 had fever and arthritis. In six patients, myalgia/arthralgia accompanied fever and abdominal pain. All of the patients (with or without current attacks) were on treatment with colchicines at a dose of 1-1.5 mg. 75% of all patients had positive family history. The mean age was 32.4±13.4 years for patients in the attack period, and 34.9±12.1 years for patients in the attack-free period. The two groups did not show a statistically significant difference with respect to age (p=0.5). There were 8 female and 12 male patients in the attack period and 17 female and 3 male patients in the attack-free period. A statistically significant difference was found in gender between the 2 groups (p=0.003 x^2=8.64). The mean duration of disease was 5.8±4.4 years for patients in the attack period and 5.1±3.5 years for patients in the attack-free period. There was not a statistically significant difference between the 2 groups in disease duration (p=0.5). Demographic and clinical findings of the patients are presented in Table 1.

25(OH) Dlevel (mean ± SD) was 17.9 ± 7.8 ng/ml for patients who were in the attack period and 14.1 ± 7.13ng/ml for patients in the attack-free period. 25(OH) D levels did not show a statistically significant difference between the 2 groups (p=0.1).25(OH) Dlevels of patients in the attack period and attack-free period are presented in Table 2.

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Mean25(OH) Dlevel was 14.1±7.6 ng/ml in female patients and 19.1±6.6 ng/ml in male patients. There was a statistically significant difference between the 2 groups in 25(OH) Dlevels (p=0.04). No significant association was found between attack frequency and 25(OH) Dlevels as assessed by Spearman's correlation analysis (r=0,27 p=0.09). However, there was a statistically significant difference in attack frequency between genders (p=0.01). Attacks recurred on a monthly basis in 72% of the female patients, whereas 60% of male patients experienced recurring attacks once in more than a month.25(OH) Dlevels and attack frequency of patients are shown in Table 3 by gender.

Discussion

In the present study, 72.5% of all patients had 25(OH) Ddeficiency and there was not a statistically significant difference between the 2 groups in 25(OH) Dlevels during attacks and attack-free periods. There was no significant association between attack frequency and 25(OH) D levels, however there was a statistically significant difference in attack frequency between genders.

FMF is characterized by recurrent episodes off ever and inflammation of serous surfaces and factors initiating inflammation and attacks are not clear (Topaloglu et al., 2010 and Karadag et al., 2013). Acute phase reactants and cytokines are elevated during FMF attacks (BerkunandEisenstein,2014 and Orun et al., 2002). Cytokines are the primary mediators involved in the production of acute phase proteins during an inflammatory event, and TNF α, IL-6 and IL-8 are the major cytokines associated with inflammation [11]. IL-6, IL-8, IL-12 and TN Fα levels are increased during FMF attacks (Rimar et al., 2012). Vitamin D is involved in the proliferation of a variety of cells of the immune system and mainly T lymphocytes (Rossini et al., 2010). Vitamin D decreases the production of proinflammatory cytokines such as IL-2, INFδ and TNF and inhibits IL-6 expression (Karadag et al., 2013). Vitamin D deficiency has been reported to be associated with a wide range of autoimmune disorders (Erten et al., 2013, Marques et al., 2010 and Kisacik et al., 2013).

Topalogluet al. explored whether there was a relationship between neuro endocrine and immune systems and acute inflammation and attacks in FMF patients. They found elevated IL-6 levels during an attack compared to those obtained during attack-free period but low ACTH and cortisol in FMF patients (Topaloglu at al., 2010).In another study, Or unit al. found elevated TNFα, IL-6 and IL-8 levels during attack period in FMF patients which were higher compared to a healthy group also during attack-free period and concluded that subclinical inflammation persisted in attack-free period (Orun et al., 2002).

A limited number of studies exist in literature on vitamin D levels in FMF patients (Erten et al., 2013, Kisacik et al., 2013 and Anık et al., 2014). Those studies have assessed vitamin D levels only during attack-free period in FMF patients. In the present study, we investigated vitamin D levels in FMF patients both during attacks and attack-free periods and sought to determine whether there is an association between vitamin D levels and attacks. Ertenet al. evaluated vitamin D levels in 99 FMF patients and 51 control subjects during attack-free period and found

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lower vitamin D levels in FMF patients versus control group. Whereas male patients did not differ from control group in vitamin D levels, female patients had markedly lower vitamin D levels versus control group (Erten et al., 2013). Our results were similar this study, our female patients had lower vitamin D levels compared to those of male patients. And in our study attacks recurred at a higher frequency among female patients versus male patients. Kisaciket al.assessed vitamin D levels in 26 FMF patients and 34control subjects and found considerably lower vitamin D levels among FMF patients compared to those of control group. They suggested that vitamin D deficiency might be a factor triggering the attacks (Kisacik et al., 2013).

In our study, we found %72.5 of our patients had vitamin D deficiency and there was neither a difference between vitamin D levels obtained during attacks and attack-free periods nor a correlation between attack frequency and vitamin D levels. So we did not find vitamin D deficiency triggered the attacks in FMF in our study.

To our best knowledge, there is no study in literature that investigated vitamin D levels in FMF patients during attacks and attack-free periods. The major limitation of our study was non-homogeneous gender distribution. Male predominance among patients presenting to the emergency department and higher vitamin D levels found in males may have influenced our results. Thus, we believe that future studies with a homogeneous gender distribution and a larger number of patients would be beneficial in evaluating the relationship between vitamin D levels, genders and attack frequency in FMF patients.

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Table1: Demographic and clinical data of patients in the attack period and attack-free period.

	Attack Period (n=20) n (%), mean±SD	**Attack-free Period (n=20) n (%), mean±SD**	**P Value**
Gender			**0,003***
Female	8 (40.0)	17 (85.0)	
Male	12 (60.0)	3 (15.0)	
Age (years)	32.4 ±13.4	34.9±12.1	0.5
Disease duration (years)	5.8 ±4.4	5.1 ±3.5	0.5
Family history			0.4
Positive	14 (70.0)	16 (80.0)	
Negative	6 (30.0)	4 (20.0)	
Attack symptoms			
Fever+Abdominal pain	11 (55.0)		
Fever+ Arthritis	3 (15.0)		
Fever+ Abdominal pain+ Myalgia	6 (30.0)		
Attack frequency			0.1
Once a week	-	-	
Once in every 15 days	4 (20.0)		
Once a month	10 (50.0)	13 (65.0)	
Once in more than a month	6 (30.0)	7 (35)	

*Statistically significant, p value: <0.05

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Table2. 25(OH)D levels of patients during an attack and attack-free period.

	Attack Period (n=20) mean±SD	**Attack-free Period (n=20) mean±SD**	**P Value**
25(OH)D ng/ml (all patients)	17.9±7.8	14.1±7.13	0.1
25(OH)D ng/ml (females)	17.5±9.7	12.5±6.1	0.1
25(OH)D ng/ml(males)	18.1±6.7	23.2±5.7	0.2

Statistically significant, p value: <0.05

Table 3.25(OH)D levels and attack frequency of patients by gender.

	Females (n=25) n (%), mean±SD	**Males (n=15) n (%), mean±SD**	**P Value**
25(OH)D ng/ml	14.1 ± 7.6	19.1 ± 6.6	**0.04***
Attack frequency			**0.01***
Once in every 15 days	3 (12.0)	1 (6.7)	
Once a month	18 (72.0)	5 (33.3)	
Once in more than a month	4 (16.0)	9 (60.0)	

*Statistically significant, p value: <0.05