Serum vitamin D levels during activation and remission periods of patients with juvenile idiopathic arthritis and familial Mediterranean fever

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The aim of this study was to determine the frequency of vitamin D deficiency and/or insufficiency in children with juvenile idiopathic arthritis (JIA) and familial Mediterranean fever (FMF) and to assess the relationship between vitamin D and disease activity. Sixty four patients with JIA, thirty six patients with FMF and one hundred healthy children were enrolled in this study. Vitamin D levels were measured during activation and remission periods in the patients with JIA and during attack and attack free periods in the patients with FMF. The mean vitamin D levels were found to be 18. 9±11 ng/ml and 18.6±9.2 ng/ml during activation and remission periods of disease, respectively, in the patients with JIA, 16±8.5 ng/ml and 13.1±6.4 ng/ml during attack and attack-free periods, respectively, in the patients with FMF and 26.7±10.5 ng/ml in the healthy children. There was no significant difference between vitamin D levels during activation and remission periods in the patients with JIA, whereas vitamin D levels during attack free periods were lower compared to attack periods in the patients with FMF. No significant relationship was found between disease activity and serum vitamin D levels. The vitamin D levels of the children with JIA and FMF were significantly lower compared to the healthy children. The frequency of vitamin D deficiency and insufficiency was considerably high among the patients with JIA and FMF.

Key words: juvenile idiopathic arthrtitis, familial Mediterranean fever, vitamin D, children, disease activity.

Hypovitaminosis D is an important public health problem and affects children all around the world. Several studies have also reported high percentages of vitamin D deficiency and insufficiency during childhood[1-4]. In addition to the role of vitamin D in bone mineralization and calcium metabolism; it has immunomodulatory effect on innate and adaptive immunity. It is speculated that abnormalities in vitamin D metabolism cause the release of proinflammatory cytokines inhibiting regulatory T cell production[5-6]. Several studies have reported a relationship between vitamin D deficiency/insufficiency and chronic autoinflammatory disorders[7-8].

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disorder in children and a significant cause of both short and long-term disabilities. It is a multifactorial inflammatory disease characterized by persistent joint inflammation which manifests as swelling, pain and limitation of movement[9-11]. The fact that vitamin D inactivates Th1 and Th17, both of which are thought to have a role in JIA pathophysiology, supports the claim that there may be a relationship between vitamin D deficiency and JIA[12,13]. However, data regarding the association between disease activity and serum vitamin D levels in children with JIA are limited.

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disorder characterized by recurrent episodes of fever and inflammation resulting in peritonitis, pleuritis, arthritis and erysipelas-like rash. Despite being the most common periodic fever, the factors triggering and terminating these spells are not completely understood[14]. In several studies, inverse correlation was found between disease activity and serum vitamin D levels in patients with FMF[15-17].

The aim of this study was to determine the prevalence of vitamin D deficiency and/or insufficiency and to investigate the relationship between vitamin D and disease activity in patients with JIA and FMF.

Material and Methods

The participants of this cross-sectional study included 64 patients who presented to the Pediatric Rheumatology outpatient clinic of Cerrahpasa School of Medicine between March 2013 and February 2014 and were diagnosed with JIA according to the classification criteria of the International League of Associations for Rheumatology (ILAR)[18] and 36 patients with FMF diagnosed using the criteria set by Yalcinkaya[19]. The control group was composed of 100 healthy children matched for age and sex.

The serum 25(OH) vitamin D levels were evaluated during activation and remission periods of disease in the patients with JIA and during attack and attack free periods in the patients with FMF. The patients who were found to have active disease with clinical and laboratory assessment were included in the study. The number of joints with active inflammation was recorded for patients with JIA. The results of the Physician Visual Analog Scale (VAS Physician) which is used by physicians to assess the general disease activity and the results of the Family Visual Analog Scale (VAS Family) which is used by patients and families to asess the general well-being were also included in the evaluation. In these scales, "0" is the best score, while "10" is the worst[20]. Age, sex, subtype of JIA, disease duration and history of use of medication were recorded. Complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) values were evaluated. The JIA patients who achieved at least ACR (American College of Rheumatology) 70 responses in the clinical follow-up were considered to be in remission. The ACR Core Data Set includes 7 measures – swollen joint

Table I. Clinical, Laboratory and Demographic Characteristics of Patients with Juvenile Idiopathic Arthritis (JIA)

	JIA (active disease) (n=64)	JIA in remission (n=53)	Healthy children (n=100)
Female/Male	41/23	35/18	50/50
Age (years)	9.7±4.3	9.8±4.3	9.9±4.1
Polyarticular JIA, n	19	15	
Oligoarticular JIA, n	33	28	
Systemic JIA,n	7	6	
Enthesitis related arthritis, n	5	4	
ESR (mm/h)	46.6±30.5* 41(25-150) * *	18.1±12.6* 15(3-30)**	
CRP (mg/dl)	3.41±3.54* 2.21 (1-15.5)**	0.78±1.54* 0.26 (0.02-3)**	
White blood cell count (mm^3)**	10,214±3,714 9,200(5,200-23,300)	8,889±2,114 9,200(5,400-12,000)	
Hemoglobin levels (g/dl)	11.1±1.7 11(6.5-15)	12.1±1.07 12(9-15)	
Thrombocyte count (/mm^3)	409,343±158,574 378,500(167,000-960,000)	317,809±114,492 322,000(168,000-682,000)	

*mean±standard deviation (SD); ** median (IQR); CPR: C-reactive protein ESR: erythrocyte sedimentation rate

count, tender joint count, patient assessment of global status, an acute phase reactant [(ESR) or (CRP)], and health professional assessment of global status, physical function, and pain. Improvement of at least 70% in both tender and swollen joint counts, and three of the five additional measures is defined as ACR 70 response. Vitamin D levels were measured during the remission period in 53 of 64 patients with JIA. Eight patients were lost in the follow–up and remission could not be achieved in 3 patients. There was no difference between activation and remission periods in terms of the medications used.

Thirty-six patients with FMF who presented with symptoms such as fever, arthritis and abdominal/chest pain and found to be in attack period with clinical and laboratory assessment (leukocytosis, elevated acute phase reactants like ESR and CRP) were included in the study. The children with FMF were screened for Mediterranean fever (MEFV) gene mutation. Sixteen patients had M694V/M694V mutation in the FMF gene, seven patients had M694V/ other genotypes (V726A, M694I, M680I, E148Q or R202Q), six patients had other/other genotypes and seven patients did not have gene mutation. The patients who had no active complaint and abnormal physical examination findings and who had normal blood values in the clinical follow-up were considered to be in the attack-free period. Six of 36 patients were lost in follow-up. All of the patients were treated with colchicine. There was no patient who was unresponsive to treatment.

Serum concentrations of calcium, phosphate and alkaline phosphatase and 25(OH) vitamin D level were measured. The 25(OH) vitamin D levels were determined in LIAISON autoanalyzer with CLIA method. The serum level <20 ng/ml (50 nmol/L) was defined as vitamin D deficiency, while between 20 and 29 ng/ml (50-72 nmol/L) was considered as vitamin D insufficiency[21]. The effect of seasonal factors on vitamin D levels were ignored. Vitamin D levels of the healthy controls were measured

Table II. Clinical, Laboratory and Demographic Characteristics of Patients with familial Mediterranean fever (FMF)

	FMF in attack period (n=36)	FMF in attack–free period (n=30)	Healthy children (n=100)
Female/Male	18/18	14/16	50/50
Age (years)	11.4±4.4	11.1±4.5	9.9±4.1
M694V/M694Vmutations, n	16	14	
M694V/Other mutations, n	7	6	
Other/Other mutations, n	6	6	
Mutation negative, n	7	4	
Fever, n (%)	22 (61.1)		
Abdominal pain, n (%)	23 (63.9)		
Arthritis, n (%)	15 (41.7)		
Erisypelas like rash, n (%)	3 (8.3)		
ESR (mm/h)	40.1±26.6* 36 (5-112)**	14.5±7.8 13.5(4-30)	
CRP (mg/dl)	8.45±6.93 7.73 (0.2-25.54)	0.46±0.77 0.1(0.02-3)	
White blood cell count (/mm^3)	11,380±4,019 104,50 (4,600-21,300)	8,659±2,127 8,300 (4,500-12,000)	
Hemoglobin levels (g/dl)	12.1±1.1 12.05 (10-14.71)	12.0±1.41 11.9 (10.2-15.7)	
Thrombocyte count (mm^3)	302,444±113,136 274,000 (132,000-665,000)	290,966±59,714 270,000 (225,000-475,000)	

*mean±standard deviation (SD); ** median (IQR)

all year round.

Statistics

The data were analyzed with IBM SPSS 19.0 (IBM Corporation 2011, NY). Categorical measurements were summarized with values and percentages, while continuous measurements were summarized with mean and standard deviation. Categorical variables were compared with Chi-square test. In comparison of the continuous variables between the groups, the Student's t-test and One Way ANOVA test were used for the parameters which showed a normal distribution and Mann Whitney U test or Kruscal Wallis test was used for the parameters which did not show a normal distribution.

The "post-hoc" evaluation of One Way ANOVA test was done with the Tukey (HSD) method. Correlation analysis was performed with Spearmen and Pearson methods. A value between 0 and 0.24 was considered weak correlation, a value between 0.25 and 0.49 was considered moderate correlation, a value between 0.50 and 0.74 was considered strong correlation and a value between 0.75 and 1 was considered very strong correlation. P values of ≤0.05 were considered significant.

This study was approved by the local ethical committee. All children and their parents were informed about the details of the study and written consent was obtained from the parents of the children involved.

Results

The mean age was 9.7±4.3 years during disease activation period in the patients with JIA, 11.4±4.4 years during attack period in the patients with FMF and 9.9±4.1 years in the control group. Forty one (64%) of the patients with JIA and 18 (50%) of the patients with FMF were female. There was no significant difference in the sex and age distribution between the groups (p=0.17 and p=0.18, respectively). The clinical and demographic characteristics of the patients with JIA and FMF are presented in Table I and Table II.

We found normal calcium, phosphate and alkaline phosphatase levels both in the healthy control group and in the patient group (data not shown). The mean vitamin D levels of the patients with JIA and FMF are given in Table III. The patient groups were divided into four groups with respect to their vitamin D levels (data are given in Table IV).

There was no significant difference between vitamin D levels of the patients with JIA during activation and remission periods, whereas vitamin D levels of the patients with FMF were lower during the attack free periods compared to the attack periods (p<0,01). There was no significant difference between the patients with JIA who were in the activation period and the patients with FMF who were in the attack period in terms of serum 25(OH) vitamin D levels (p=0.37). The serum 25(OH) vitamin D levels in the attack free periods in the patients with FMF were found to be significantly lower compared to the values found in the remission periods in the patients with JIA (p=0.007). Serum 25(OH) vitamin D levels of the healthy

Table III. Mean Vitamin D Levels of Patients with JIA (in activation and remission period) and FMF (attack and attack free period)

	Vitamin D levels (ng/ml)
JIA (Activation period) (n=64)	18.9±11 16.5(4.6-45)
JIA (Remission period) (n=53)	18.6±9.2 17.05(5.45-55)
FMF (Attack Period) (n=36)	16±8.5 12.5(4.8-38)
FMF (Attack free period) (n=30)	13.1±6.44 11.15(5-27.9)
Control Group (n=100)	26.71±10.54 27.2(6.8-61.3)

subjects were significantly higher compared to the patient groups ($p<0.01$).

There was no statistically significant correlation between the vitamin D levels and ESR and CRP levels ($r=0.2$, $p=0.08$; $r=0.08$, $p=0.5$, respectively) in the patients with JIA. There was also no statistically significant correlation between vitamin D levels and the number of joints with active arthritis ($r=0.1$, $p=0.4$) and physician and family VAS assessments ($r=0.03/p=0.77$, $r=0.03/p=0.78$ respectively). No relationship between the drug regiments [steroids, disease modifying antirheumatic drug (methotrexate, sulfasalazine, leflunamide) TNF-alpha antagonist, new generation biologic drugs (IL-1 antagonist, IL-6 antagonist, T-cell antagonist)] and vitamin D levels could be shown ($p=0.77$, $p=0.6$, $p=0.1$, $p=0.26$ respectively).

There was no statistically significant correlation between vitamin D levels and ESR and CRP levels in the patients with FMF ($r=0.02/p=0.8$, $r=-0.3/p=0.06$, respectively). No significant relationship was found between disease activity and serum vitamin D levels for both disease ($p>0.05$).

A high prevalence of vitamin D deficiency and insufficiency was found both in the patient groups and healthy control group as shown in Table IV.

Discussion

The present study showed that serum 25(OH) vitamin D levels in both activation and remission periods were significantly lower in the patients with JIA compared to the healthy controls. Pelajo et al.[22] reported that there was no correlation between JIA disease activity and serum 25(OH) vitamin D levels. They suggested that several aspects such as drug regiments which modify the disease course, vitamin D supplements and limited exposure to sunlight due to long-term restriction of movement might affect vitamin D levels. Similarly, we did not find any correlation between disease activity and serum 25(OH) vitamin D level. Furthermore, there was no correlation between vitamin D levels and the parameters used in assessing the disease activity (CRP, joints with arthritis, VAS) and drug regimens. Munekata et al.[23] did not find a significant difference between healthy children and children with JIA in terms of vitamin D levels and therefore could not associate disease activity with vitamin D level. However, they detected high levels of vitamin D deficiency and insufficiency in healthy children and patients (deficiency was found with a rate of 26.7% and insufficiency was found with a rate of 46.7% in the patients with JIA; deficiency was found with a rate of 16.7% and insufficiency was found with a rate of 60% in the healthy children). In a cross-sectional study conducted by Bouaddi et al.[24] with Moroccan children, 75% of the patients with JIA were found to be vitamin D deficient. However, no correlation was demonstrated between vitamin D level and disease activity. On the other hand, several studies conducted with RA patients showed an inverse correlation between disease activity and serum vitamin D level[25-31].

Low levels of vitamin D levels in JIA patients may arise from limited exposure to sunlight caused by restriction of movement. Loss of appetite and insufficient alimentation due to

Table IV. Vitamin D Levels of Patients with JIA (in activation and remission period) and FMF (attack and attack free period)

		JIA (Activation period) (n=64)	JIA (Remission period) (n=53)	FMF (Attack period) (n=36)	FMF (Attack free period) (n=30)	Control Group (n=100)
Vitamin D levels (ng/ml)	<10	9 (14.1%)	5 (9.4%)	10 (27.8%)	13 (43.3%)	4 (4%)
	10-20	28 (43.8%)	26 (49%)	15 (41.7%)	12 (40%)	22 (22%)
	20-30	19 (29.7%)	18 (33.9%)	7 (19.4%)	5 (16.6%)	33 (33%)
	>30	8 (12.5%)	4 (7,5%)	4 (11.1%)		41 (41%)

disease may also be a contributing factor. In this study, we prefered not to include parameters such as daily physical activity capacities, clothing styles, exposure to sunlight, eating habits, adherence to vitamin D supplement regime, which may all affect vitamin D levels.

There was no difference between vitamin D levels during activation and remission periods in the patients with JIA. This result may point out that there is no correlation between disease activity and serum vitamin D level. Our study did not find any correlation between serum 25(OH) vitamin D level and disease activity in the children with JIA. Vitamin D levels were measured at two different points of time including the activation and remission periods. This may have caused seasonal factors to come into effect and prevent the demonstration of such a correlation.

We did not observe any effect of the immunosuppressive and biological agents on serum 25(OH) vitamin D levels in children with JIA. Some studies conducted in adult patients suggest no effect of anti-inflammatory therapy on vitamin D level[25].

In the present study, serum 25(OH) vitamin D levels in the children with FMF were significantly lower compared to healthy children. The mean vitamin D level during attack free period was lower compared to the attack period. We attributed these findings to seasonal changes, because the serum vitamin D levels were measured in the attack free period (approximately two and a half months after the attack period) which coincided with winter months. No correlation between vitamin D level and disease activity could be established in the patients with FMF.

We detected high levels of vitamin D deficiency and insufficiency in our patients with FMF, but our sample size makes it hard for us to comment on possible contributing factors. Few studies have investigated vitamin D levels in patients with FMF. Recent studies have found lower serum vitamin D levels in patients with FMF compared to healthy controls which is consistent with our results[15-17]. Anık et al.[32] found significantly lower serum vitamin D levels in patients with FMF compared to the healthy children. However, a high prevalence of vitamin D deficiency in the healthy controls was also found (72% and 46% in patients and healthy controls, respectively). The authors attributed the low levels of vitamin D in patients with FMF primarily to the dose and duration of the colchicine regimen which alters vitamin D metabolism or decreases absorption of vitamin D from the gastrointestinal tract.

It is not known whether vitamin D deficiency in patients with FMF is the cause or the result. New studies with larger sample sizes investigating the relationship between FMF and vitamin D are warranted. The fact that our study was cross-sectional might have prevented demonstration of this relationship.

In conclusion, hypovitaminosis D affects children worldwide. Healthy children also have a high prevalence of vitamin D deficiency and insufficiency. The serum 25(OH) vitamin D levels were found to be significantly lower in children with JIA and FMF compared to healthy children. The frequencies of vitamin D deficiency and insufficiency were considerably high among the patients with JIA and FMF. However, no clear evidence exists supporting a link between disease activity and serum vitamin D levels. Future meta-analytic studies are required to address the role of vitamin D in rheumatic and autoinflammatory disorders.

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