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Serum vitamin D level in Egyptian children with Familial Mediterranean fever

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ABSTRACT

Background: The aim of the study is to measure plasma vitamin D levels in a group of Egyptian children with familial Mediterranean fever (FMF) compared to healthy children.
Methods: The study enrolled 52 children with FMF and 40 apparently healthy controls. Serum vitamin D level was measured by enzyme-linked immunosorbent assay.
Results: The mean serum vitamin D level was significantly lower in children with FMF than control group (12.3 ± 3.4 and 21.2 ± 3.5 ng/mL, respectively, $p < 0.001$). Vitamin D level was significantly lower in female patients than males (11.3 ± 2.9, 13.2 ± 3.6, respectively $p = 0.04$). No statistically significant relations were detected between vitamin D level and different clinical, laboratory and genetic variables.
Conclusion: Vitamin D levels were lower in Egyptian FMF children than healthy controls. There is a speculation that vitamin D deficiency in FMF patients may be related to inflammation. Further studies with larger number of patients before and after Vitamin D, therapy may be needed. Supplementation with high doses of vitamin D seems appropriate for children with FMF.

1. Introduction

FMF (MIM 249100) which is an autosomal recessive periodic fever syndrome is most common among hereditary recurrent inflammatory disorders [1]. The disease affects populations of Mediterranean descent; Arabs, Armenians, Turks, non-Ashkenazi,other Jews, Druzes, Lebanese, Italians, and Greeks. Patients have also been described in Japan [2].

The disease is characterized by recurrent flares of systemic inflammation presenting as fever associated with a number of clinical manifestations and a dramatic rise in acute phase reactants. Rash, serositis (peritonitis, pleuritis), lymphadenopathy and arthritis are the main associated clinical manifestations [3]. Disease flares are usually separated by symptom-free intervals of variable duration [4]. Mediterranean fever gene (MEFV); responsible for FMF is located on the short arm of chromosome 16 and encodes pyrin; a protein that has a role in suppression of inflammation. Mutations in MEFV gene cause uncontrolled innate immune response through overproduction of interleukin-1β and tumor necrosis factor-α [5]. Inflammation is the main pathology in FMF attacks and some patients experience it even in attack-free periods. This chronic inflammation may cause complications such as splenomegaly, anemia, decrease bone mineral density, growth retardation and amyloidosis [6].

Vitamin D is a fat-soluble vitamin with a fundamental role in calcium metabolism. Exposure of the skin to the UVR of the sun is a major source of Vitamin D in the body. After hydroxylation in the liver and kidney, the active metabolite (1,25dihydroxy vitamin D) can enter the cell, bind to the vitamin D-receptor and mediates calcium absorption from the gut [7]. It also modulates adaptive immunity to minimize inflammation and autoimmunity [8] .Moreover it helps proliferation of inhibitory T-cells and shift towards T-helper 2 response, which produces suppressive IL-10 and IFN-γ [9]. Thus, a compromised vitamin D status was linked to the pathogenesis of many inflammatory diseases [10], such as SLE [11], JIA [12], and Behcet's disease [13] .Few researches have studied serum vitamin D level in children with FMF compared with healthy controls [14–16].

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Vitamin D deficiency is a worldwide problem especially in the Middle East, with a Prevalence of Vitamin D deficiency ranging between 30 and 90% when the cut-off used is 20 ng/mL [17,18]. The aim of the present study was to measure plasma vitamin D levels in Egyptian children with FMF compared to healthy controls and study its effect; if any; on disease severity, subclinical inflammation.

2. Patients and methods

This cross sectional study enrolled 92 children, 52 patients diagnosed as FMF according to criteria defined by Yalcınkaya et al. [19]. All patients were following up at the Pediatric Rheumatology Clinic, Specialized Children Hospital of Cairo University during the period from October 2014 to October 2015. Forty apparently healthy children, age-, gender and body mass index (BMI) matched, coming for regular follow-up at the outpatient clinic were also included.

None of our patients had chronic renal or hepatic failure, malnutrition and metabolic bone disease. Patients receiving any drug known to affect vitamin D levels including regular anticonvulsant therapy were excluded from the study. The study was approved by the Cairo University Clinical Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Informed consents were obtained from parents of all participants.

Demographic, clinical and laboratory characteristics of the patients were evaluated at the time of study enrollment. Data collected included: age at diagnosis, FMF manifestations, disease duration, colchicine dosage and duration, and disease severity score.

Samples were collected during autumn and winter season to minimize the effect of sunlight on vitamin D level. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and urinalysis were determined by the standard laboratory methods at the time of study. The results of MEFV gene mutations testing were obtained from the patients' files. Prasetal, 1998, calculated the disease severity according to the scoring system [20].

2.1. Measurement of serum vitamin D

Samples for vitamin D measurement were collected from all patients at least 2 weeks after the last attack. Patients receiving low doses of colchicine due to intolerance mainly due to diarrhea and those with low compliance due to social or economic factors were not excluded from the study.

For vitamin D measurement, blood samples were withdrawn from patients and controls after an overnight fasting and left to clot for 15 min then centrifuged at 14,000 rpm for 10 min. The separated serum was then kept frozen at −80 °C until analysis. Serum samples were examined for 25 OH vitamin D levels by enzyme-linked immunosorbent assay (ELISA) by kit supplied by (Immunodiagnostic USA) briefly; monoclonal antibody identifying 25, OH vitamin D. The samples were incubated with the detection antibody after the extraction step. Then peroxidase-conjugated anti-mouse antibody was then added into micro plate well, forming a complex of 25-hydroxy vitamin D – detection antibody – peroxidase conjugate. Tetramethylbenzidine (TMB) was used as a substrate, the color density developed is proportional to vitamin D concentration. Finally, to terminate the reaction, stop solution was added and the micro plate was read by ELISA reader at 520 nm. Usually the reference intervals for vitamin D metabolites depend on the method of measurement [21]. For the present work serum Vitamin D mild-moderate deficiency was considered between, 10–24 ng/mLand severe deficiency, 0–10 ng/mL.

2.2. Statistical analysis

Data analysis was performed through Statistical Package of Social Sciences (SPSS) software program for windows version 21. Data was expressed as mean and standard deviation for quantitative variables and number and percentage for qualitative ones. Comparison between serum vitamin D level in patients and control was performed through Chi square test. Mann–Whitney test was used for comparison of serum 25(OH) D3 levels according to the clinical manifestations in FMF. Spearman correlation coefficients were calculated to signify the association between different quantitative variables. P values less than 0.05 were considered significant.

3. Results

The study included 52 Egyptian children with FMF, and 40 apparently healthy controls. Twenty-eight patients were males and 24 were females (male to Female ratio 1.16:1). The mean age at diagnosis was 6.4 ± 3.2 years. The mean disease duration was 4.3 ± 2.8 years (range 0.3-12.0 years). Parents of (32.7%) of patients were consanguineous. The demographic and the presenting FMF manifestations of the study group were summarized in Table 1.

The most frequent clinical manifestations of FMF attacks were abdominal pain in 51 patients (98%) followed by fever, arthralgia and chest pain (Table 1).

The mean serum vitamin D level (ng/ml) was significantly lower in children with FMF than control group (12.3 ± 3.4 and 21.2 ± 3.5 ng/mL, respectively, $p < 0.001$) (Table 2).

Table 1
Demographic data, presenting manifestations and severity score of FMF study group.

Variable	FMF patients (n = 52) (Mean ± SD)/frequency
Demographic data	
Age at diagnosis (years)	6.4 ± 3.2
Disease duration(years)	4.3 ± 2.8
Male/Female ratio	28/24
Duration of attacks/day	1.7 ± 1.8
Colchicine duration(years)	2.1 ± 2.3
Colchicine dosage (mg)	1.0 ± 0.4
Clinincal manifestations	
Abdominal pain	51(98%)
Fever	47(90.4%)
Arthralgia	44(84.6%)
Chest pain	37(71.2%)
Myalgia	19(36.5%)
Arthritis	15(28.8%)
Rash	6 (11.2%)
Vasculitis	2 (3.8%)
Laboratory manifestations	
Proteinuria	11 (21.2%)
Vitamin D level (ng/ml)	12.3 ± 3.4
CRP titer	12.0 ± 8.3
ESR	33.4 ± 19.8
Hb	12.1 ± 1.0
TLC	7.6 ± 3.0
Platelet	326.2 ± 81.2
Allelic frequency of MEFV mutations[a]:	
V726A	19 (36.5)
M694I	19(36.5)
M694V	13(25.0)
M680I	10(19.2)
E148Q	9(17.3)
Severity score:	
Mild	10(19.2)
Moderate	9(17.3)
Severe	33(63.5)

[a] Including heterozygous, homozygous and compound heterozygous mutations.

Table 2
Vitamin D levels in FMF patients and controls.

Variable	FMF patients (n = 52)	Controls	P value
Serum vitamin D level (Mean ± SD) (ng/ml)	12.3 ± 3.4	21.2 ± 3.5	p < 0.001

Vitamin D levels were significantly lower in female patients than males (11.3 ± 2.9, 13.2 ± 3.6, respectively, p = 0.04)

Vitamin D level was significantly correlated with level of HB (r = −0.314, p = 0.023). On the other hand, no significant correlations were detected between vitamin D level and age of patients, disease duration, duration before diagnosis, disease severity score, colchicine dosage and duration, serum CRP and ESR (Table 1s).

When stratified according to the presence or absence of different clinical, laboratory, genetic variables and severity scores, no statistically significant relations were detected. Although serum 25(OH) D3 levels were lower in FMF patients with recurrent erythematous rash, vasculitis and in those with history of appendectomy; the relations were not statistically significant. Plasma vitamin D levels were similar among FMF patients with different *MEFV* mutations ($P > 0.05$) (Table 3). The most common Allelic MEFV mutations detected were V726A ($N = 19$, 36%) and,M694I ($N = 19$, 36%).Yet, it is worth noting that serum vitamin D levels were lower in patients carrying V726A and M680I mutations and in patients with scores above 3 in the severity score by Pras et al. Table 3.

4. Discussion

This study was able to detect a significant decrease in the serum level of vitamin D in children with FMF compared to the control group.

No significant correlation was detected between vitamin D level and acute phase reactants. This was in concordance with the results of Anik et al. [14] showing insignificant correlation between serum vitamin D level and acute phase reactants. Our patients displayed a much higher titer of CRP (12 ± 8.3 versus 4.7 ± 8.7) either due to low colchicine dose tolerated by patients, or incompliance due to social or economic factors.

Decreased serum vitamin D level was also reported by Erten and colleagues in a study on adults with FMF [22]. These results partially agreed with the present work, since they reported a significant correlation between the drop in vitamin D serum level and the rise of acute phase reactants. This disagreement might be attributed to their enrollment of more patients compared to our relatively small sample. Difference in age between the studied groups might also explain such discrepancy. A similar remarkable decrease was detected in another study in adults with FMF [23].

Our study did not find any significant correlation between serum levels of vitamin D and the colchicine dose or duration of treatment. On the other hand, while a similar hypovitaminosis D was reported by a recent study in children with FMF [11] a disparity lied in their reporting of a significant relation of the decrease in vitamin D levels and the colchicine therapy. They proceeded further to speculate that such drop in vitamin D level might be an unwanted side effect of colchicine treatment since it causes defects in the micro tubular network. This was specifically documented in other studies [24,25].

Vitamin D deficiency was also reported to be related to diarrhea accompanying colchicine therapy in children. Padeh et al.reported that 14% of patients developed diarrhea during colchicine treatment [26]. However, such assumption could not apply for our study since our results did not find any correlation with colchicine therapy.Additionally some of our FMF study group tend to take the maximum tolerated dose causing minimum diarrhoea; even if lower than the dose causing complete control. The lack of correlation with colchicine dose and duration of treatment was not in concordance with the results of Karatay et al. [27] where they found that the decrease in serum vitamin D level was strongly correlated with the colchicine treatment in adult Behcet's patients.

The present study detected decrease in serum vitamin D in FMF patients with more severe disease course, but with no statistical significance. Similarly, Yilamazetal, [15] failed to find a significant correlation between vitamin D and disease severity.

Table 3
Correlation between serum 25(OH) D3 level and clinical manifestations, CRP level, severity score and different MEFV gene mutations.

Variable (n = 52)	Serum 25(OH) D3 levels mean (SD), ng/ml		P-value
	Variable present	Variable absent	
Fever	12.5 ±3.5	11.1 ± 1.0	0.4
Abdominal Pain	12.4 ± 3.4	10.3(only one case)	0.6
Chest pain	12.3 ± 3.7	12.5 ± 2.6	0.8
Myalgia	12.1 ± 3.3	12.4 ± 3.4	0.8
Arthritis	12.9 ± 2.6	12.1 ± 3.6	0.4
Rash	11.8 ± 2.5	12.4 ± 3.5	0.7
Vasculitis	11.4 ± 1.5	12.4 ± 3.4	0.7
Testicular affection n = 28	12.4 ± 3.8	13.3 ± 3.6	0.6
Appendectomy	10.6 ± 1.3	12.5 ± 3.5	0.3
Adherence	12.1 ± 3.3	12.6 ± 3.6	0.6
Proteinuria	12.8 ± 3.9	12.2 ± 3.3	0.8
MEFV gene mutation			
Heterozygous	12.8 ± 3.8		0.6
Homozygous	12.2 ± 3.0		
Compound heterozygous	11.7 ± 3.1		
V726A	11.4 ± 2.4	12.9 ± 3.7	0.08
M694I	12.0 ± 3.2	12.5 ± 3.5	0.7
M694 V	12.4 ± 3.7	12.3 ± 3.3	0.9
M680I	11.9 ± 3.7	12.4 ± 3.3	0.7
E148Q	13.2 ± 4.5	12.1 ± 3.1	0.5
CRP	13.1 ± 3.6	12.0 ± 3.3	0.3
Severity score			
Mild	14.1 ± 4.7		0.2
Moderate	12.0 ± 3.6		
Severe	11.9 ± 2.7		

Female patients had a significantly lower vitamin levels than male patients. This may be related to the fact that females in the Middle East wear more clothes and are less involved in outdoor activities due to traditional and religious causes [28].

1 More reduction in Vitamin D levels were not detected in patients with articular manifestations, despite the role played by vitamin D in calcium homeostasis. Our results were in concordance with the study of Onur et al. [16], with no significant relation detected between vitamin D level and the presence of articular manifestations. On the contrary, Erten et al. [22]. found a significant relation between vitamin D levels and articular manifestations in adult FMF patients. These differences may be related to differences in patient age and presence of other co morbid conditions in adults [16] Association between Vitamin D and anemia in various healthy and diseased populations was previously reported [29].

In our work Vitamin D level was significantly correlated with haemoglobin level ($p = 0.023$). This may be related to inflammation caused by FMF, or associated with vitamin D deficiency through reduction of proinflammatory cytokines by vitamin D and the direct suppression of hepcidin mRNA transcription [29].

Early experimental studies on murine models of systemic lupus erythematosus were able to prove improvement of some of the disease manifestations following administration of vitamin D [30].

Whether vitamin D deficiency is a trigger factor or a side effect remains an area for research. However, it appears that whatever it was, the patient would benefit from substituting the deficit.

Limitations in the present study were the relatively small number of patients and lack of information about clothing habits, dietary habits and exposure to sunlight, which can affect vitamin D level in the body.

To our knowledge, the majority of studies carried on this subject were mostly on adult patients and only few studies done on children [16,14].

This draws concern for the necessity to investigate the serum vitamin D levels in FMF children on a larger scale for better understanding of the relevance with disease, which may affect the disease management.

In conclusion, vitamin D deficiency is a major problem in the Middle East and its deficiency in children with FMF is even more marked. Whether vitamin D deficiency is a trigger factor or a side effect remains to be elucidated. Instructing children with FMF about the importance of exposure to sunlight, food rich in vitamin D and supplementation with high doses of vitamin D seems very beneficial for them.

Conflict of interest

The authors declare that they have no conflict of interest.

Contribution

Prof. Dr. Hala M Lotfy: supervision of data collection, revision of the statistical analysis of the results, writing and revising the manuscript, and corresponding for publication.

Dr. Huda Marzouk: idea, data collection, revision of the statistical analysis of the result, writing and revising the results, revising the manuscript.

Dr. Yomna Farag: data collection, revision of the statistical analysis of the results, writing and revising the manuscript.

Dr. Ahmed Salah: revision of results and statistical Analysis, writing and revising the manuscript.

Dr. Heba Taher: supervision of data collection, revision of the manuscript.

Dr. Mohammad Nabih: supervision of data collection, revision of the manuscript.

Prof. Dr. Rashed L.A.: performance and supervision of laboratory investigations, revision of manuscript.

Dr. Kamal El Garf: Revision of the statistical analysis of the results, contribution in writing the results revision of manuscript.

Ethical approval

The Cairo University Clinical Research Ethics Committee approved this study, and informed consents were obtained from parents of all participants.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.imlet.2017.03.001.

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