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Journal of Clinical Pediatrics and Care
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ISSN: 2836-8630 RESEARCH ARTICLE

Serum Vitamin D Levels In Pediatric Patients With Familial Mediterranean Fever

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Received Date: 24 May 2024; **Accepted Date:** 04 June 2024; **Published date:** 10 June 2024

Citation: Ahmet Ibrahim KURTOGLU, et.al., (2024). Serum Vitamin D Levels In Pediatric Patients With Familial Mediterranean Fever. Journal of Clinical Pediatrics and Care. 3(1); DOI: 10.58489/2836-8630/011

Abstract

Introduction: Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder. Vitamin D deficiency is a common finding in patients with various chronic inflammatory diseases. Several studies have elucidated the correlation between serum vitamin D levels and disease activity in pediatric Familial Mediterranean Fever patients. In this study, we aimed to investigate the role of vitamin D in the development of Familial Mediterranean.

Method: This study includes 95 pediatric patients diagnosed with Familial Mediterranean Fever who were followed by the Department of Pediatrics at an Application and Research Hospital in Turkey and agreed to participate in the study. Additionally, 34 healthy children who consented to participate constituted the control group. The diagnosis of patients with FMF utilized the Tel-Hashomer criteria

Results: The hormone levels of FMF and control groups were compared. Vitamin D levels, calcium, phosphorus, Parathyroid Hormone and Alkaline Phosphatase levels were analyzed. In the FMF group, the Vitamin D level was found to be significantly lower, while the Ca and phosphorus levels were significantly higher compared to the control group (both with $p<0.01$). Although the difference in Ca levels between the two groups was statistically significant, the mean Ca levels of both groups remained within the normal range.

Conclusion: In conclusion, the significant deficiency of serum vitamin D levels in pediatric FMF patients and its association with disease severity underscores the importance of regular monitoring and potential therapeutic intervention.

Keywords: *Familial Mediterranean Fever, Vitamin D deficiency, Calcium, Autoimmunity, Bone mineral density.*

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disorder predominantly affecting populations of Mediterranean descent [1]. Characterized by recurrent episodes of fever and serositis, FMF often manifests in childhood, significantly impacting the quality of life of pediatric patients. Recent research has increasingly focused on the potential role of vitamin D, a secosteroid hormone essential for calcium homeostasis and immunomodulation, in the pathophysiology of FMF [2].

Vitamin D deficiency is a common finding in patients with various chronic inflammatory diseases, including FMF. The etiology of this deficiency in FMF patients is multifactorial. FMF is associated with mutations in the MEFV gene. The MEFV gene encodes the protein "pyrin." These mutations are linked to the uncontrolled production of interleukin-1 and the resultant inflammatory response [3]. Chronic inflammation, decreased sun exposure due to lifestyle changes during flare-ups, and potential genetic predispositions may contribute to lower serum vitamin D levels [4]. Additionally, medications such as colchicine, the cornerstone of FMF

management, might interfere with vitamin D metabolism, further exacerbating the deficiency [5].

Several studies have elucidated the correlation between serum vitamin D levels and disease activity in pediatric FMF patients [6–8]. These studies often employ the measurement of 25-hydroxyvitamin D [25(OH)D], the primary circulating form of vitamin D, to assess vitamin D status. It has been observed that pediatric patients with active FMF tend to have significantly lower levels of 25(OH)D compared to those in remission and healthy controls [8,9]. This deficiency may be linked to the pro-inflammatory state of FMF, as vitamin D is known to exert anti-inflammatory effects through the inhibition of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α [8,10].

The clinical implications of vitamin D deficiency in FMF are profound. Vitamin D not only plays a crucial role in bone health but also modulates immune responses, which could influence the severity and frequency of FMF attacks [11]. Hence, addressing vitamin D deficiency in pediatric FMF patients may offer a therapeutic avenue to mitigate disease activity and improve overall health outcomes. The severity of the disease and the overall outcome are determined by various criteria such as symptom classification, clinical grading, cognitive function assessments, dietary intake, and food frequency questionnaires, complete blood count, and C-reactive protein levels [11].

To this end, routine screening for vitamin D levels in pediatric FMF patients is recommended [12]. Supplementation strategies should be tailored to individual needs, considering factors such as baseline vitamin D levels, seasonal variations, and potential drug interactions. Furthermore, the implementation of dietary modifications and lifestyle interventions to enhance vitamin D synthesis and absorption should be emphasized [13].

In this study, we aimed to investigate the role of vitamin D in the development of Familial Mediterranean Fever (FMF) or in the triggering of its attacks.

Material and Methods

Study Design and Participants

This study includes 95 pediatric patients diagnosed with FMF who were followed by the Department of Pediatrics at an Application and Research Hospital in Turkey and agreed to participate in the study. Additionally, 34 healthy children who consented to participate constituted the control group. Our study participants are within the pediatric age group. The diagnosis of patients with FMF utilized the Tel-Hashomer criteria. Tel-Hashomer is a diagnostic method based on the presence of criteria such as recurrent febrile episodes, amyloidosis, and response to regular colchicine treatment [14]. Participants who consented to partake in the study were included regardless of their treatment durations. The control group comprised individuals with no chronic illnesses or personal or familial histories of FMF. In a study investigating the impact of breastfeeding on the severity of FMF, no correlation was found between the duration of breastfeeding and the clinical presentation of FMF in children [4].

Examined Variables

- 25-hydroxyvitamin D (25(OH)D) Level,
- Parathyroid Hormone (PTH),
- Alkaline Phosphatase (ALP),
- Calcium (Ca),
- Phosphorus,
- Living Conditions,
- Place of Residence,
- Presence of Familial Mediterranean Fever (FMF) in Family Members,
- Child's Gestational Age at Birth,
- Frequency of Infections in the Child,
- Maternal Habits During Pregnancy,
- Paternal Habits,
- Height and Weight Percentiles.

Exclusion Criteria

- Participants who refuse to participate in the study

Ethics

Ethical permissions for the research were obtained from the relevant boards of the institution where it was conducted. Participation is voluntary. Informed consent was obtained from the participants. Personal data and identities were kept confidential. The entire study was conducted in accordance with the principles outlined in the latest version of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using the SPSS statistical software. The chi-square test was employed for comparing nominal data. An independent samples t-test was utilized to compare serum vitamin D levels. Additionally, a Spearman correlation analysis was conducted to examine the difference in vitamin D levels between genders.

Results

Among the children participating in the study, 79 were female and 50 were male. The gender and age distributions between the patient and control groups were similar, with no significant differences observed between the groups (p=0.55 and 0.68, respectively). Nearly all participants were born in the Mediterranean region. When the vaccination status of the participants in the FMF group was examined, it was found that only one participant had incomplete vaccinations. The average weight of this group was 23.2±3.4 kg, the average height was 124.5±20.7 cm, and the average number of siblings was three. The mean duration of exclusive breastfeeding was 5.6±2.9 months, and the total duration of breastfeeding was 13.3±9.6 months. The average duration of colchicine use was 12 months, with an average dosage of one gram. Additionally, 16.8% of the participants in the FMF group were below the third percentile.

The gestational weeks and infection histories of the FMF group have been examined and determined to show no distinctive features. Of the participants, 89% have working mothers. Two participants have deceased mothers. The average duration of maternal education is 7.78±2.42 years. In the FMF group, the mean maternal age is 33.0±8.3 years, and the mean maternal weight is 71.3±13.8 kg. Additionally, 12.6% of the mothers smoked during pregnancy.

Within the FMF group, consanguineous marriage was present in 12 families (12.6%). In 58.9% of the group, there were no other FMF patients in their families, with the family disease status detailed in Table 1. Seven mothers in the FMF group are FMF patients themselves, and 22 children have mothers with chronic illnesses, three of which are due to FMF-associated chronic renal failure. The levels of Vitamin D in patients with chronic illness and chronic renal failure are significantly lower compared to those with FMF (34.26±7.34 mg/dl and 14.09±2.72 mg/dl, respectively). Nine participants (9.4%) had both parents afflicted with chronic illnesses. The vitamin D levels of parents with chronic diseases were comparable to those of the other parents.

Regarding the fathers in the FMF group, 33 (34.7%) have a chronic illness, and three children's fathers are deceased. The average paternal age is 39.2±8.4 years, with an average weight of 83.1±12.8 kg and an average education duration of 8.26±2.26 years.

Table 1: Presence of FMF in the families of the FMF group.

FMF in the families	Frequency	%
None	56	58,9
Father/Mother	7	7,4
Brother/Sister	19	20,0
Uncle, Aunt	9	9,5
Cousin	4	4,2
Total	95	100,0

The hormone levels of FMF and control groups were compared. The analyses of Vitamin D levels, Ca, phosphorus, ALP, and PTH levels are presented in Table 2. In the FMF group, the Vitamin D level was found to be significantly lower (p<0.01), while the Ca levels were higher compared to the control group. The difference in Ca levels between the two groups was not significant statistically, the mean Ca levels of both groups remained within the normal range. Vitamin D and calcium levels are illustrated in Figure 1. In this study, vitamin D deficiency among participants is attributed to low levels of both vitamin D and calcium.

Table 2: Vitamin D, Ca, phosphorus, PTH, ALP levels.

	Group	Sayı	Mean±SD	p
Vitamin D (25(OH)D)	FMF	95	54,76±17,15 mg/dl	**<0.01**
	Control	34	73,17±21,80 mg/dl	
Ca	FMF	95	10,01±0.45 mg/dl	**0.34**
	Control	34	9,69±0.59 mg/dl	
Phosphorus	FMF	95	4,82±0.51 mg/dl	0,20
	Control	34	4,69±0.54 mg/dl	
ALP	FMF	95	203,52±70.29 IU/L	0,07
	Control	34	228,50±70.63 IU/L	
PTH	FMF	95	52,02±28.07 pg/ml	0,07
	Control	34	50,43±17.27 pg/ml	

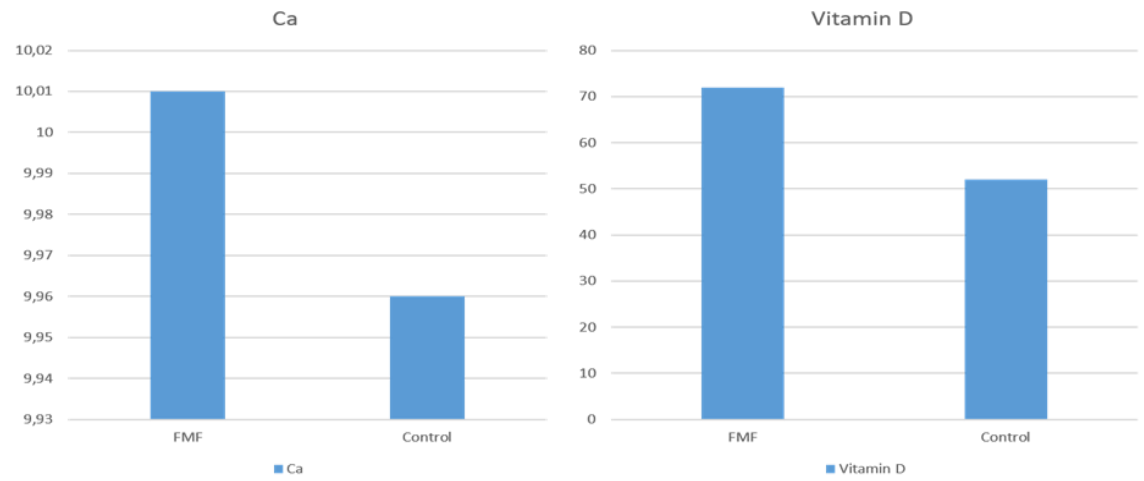

Fig 1: Vitamin D and Ca levels in FMF and Control Groups.

No correlation was found between Vitamin D levels and age, weight, or height in the entire population (with p-values of 0.3, 0.7, and 0.6, respectively). There was no correlation between Vitamin D levels and gender. The presence of FMF in the family was not identified as a risk factor for Vitamin D deficiency (OR: 0.52, p: 0.15). No correlation was detected between serum Vitamin D and Ca levels and the duration of breastfeeding (with p-values of 0.2 and 0.8, respectively). There was no correlation between age and serum Ca levels (p=0.2). However, children of mothers who smoked during pregnancy had significantly lower serum Ca levels (p=0.02), as depicted in Figure 2.

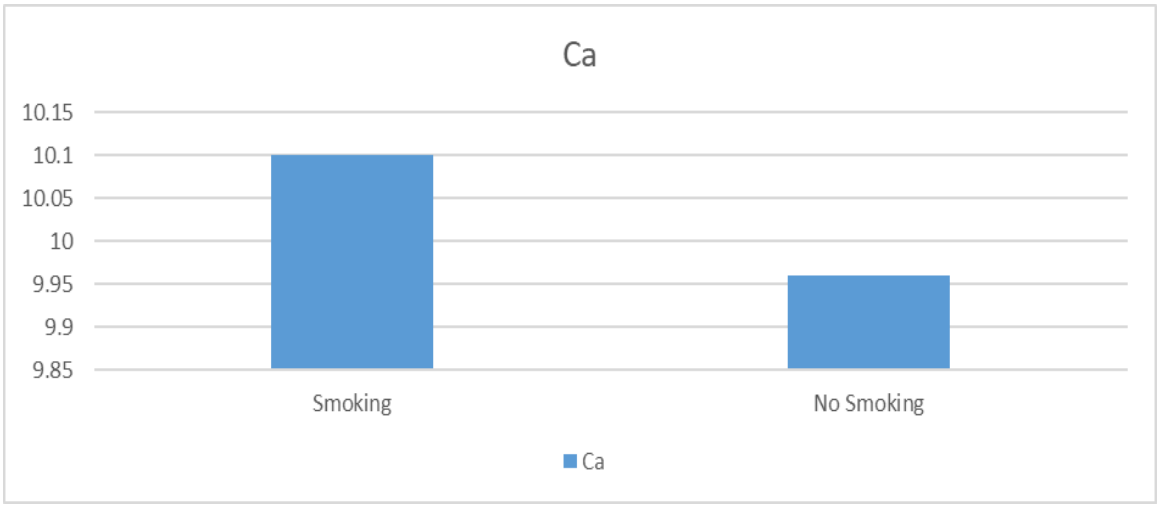

Fig 2: Calcium Levels in Children of Smoking and No-Smoking Mothers

Discussion

In a study conducted by Adams and colleagues in 1983, involving seven patients with sarcoidosis and two patients with idiopathic pulmonary fibrosis, the effects of active vitamin D on the immune system and its significance in autoimmune diseases were highlighted [15]. Rigby and colleagues, in their 1984 study, demonstrated that vitamin D increases phytohemagglutinin and suppresses IL-2, thereby emphasizing its immunomodulatory role [16]. Following these two pivotal studies, the relationship between vitamin D and autoimmune diseases has been extensively investigated [17,18].

It has been shown that low levels of vitamin D are associated with an increased incidence of osteoarthritis [19], rheumatoid arthritis [20], multiple sclerosis [21], and diabetes mellitus [22]. Active vitamin D and its analogs have been demonstrated to prevent lupus-like symptoms and reduce the development of inflammatory bowel disease [23]. In cases of multiple sclerosis, vitamin D supplementation has been found to decrease pro-inflammatory cytokines while increasing the release of anti-inflammatory cytokines [21]. Epidemiological studies in regions with ample sunlight exposure, where the prevalence of multiple sclerosis is low, suggest that an optimal serum vitamin D level of over 400 IU is necessary for protection against multiple sclerosis [24]. To achieve this serum level, it is

recommended that individuals deprived of sunlight intake 100 micrograms of vitamin D daily [25].

All these studies, suggest that vitamin D deficiency may play a significant role in the onset, severity, and management of FMF.

In a manner similar to previous studies, our research also indicates that vitamin D levels are lower in the FMF group compared to the control group. Additionally, a significant proportion of height percentiles fall below the third percentile. These data underscore the importance of vitamin D in the context of FMF.

Various studies have demonstrated that patients with FMF exhibit significantly reduced bone mineral density in regions such as the vertebrae and femur [26–28]. It was documented that vitamin D suppresses immunoglobulin production, reduces the release of cytokines such as IL2 and TNFα, which play a key role in autoimmunity through Th1 cells, and delays B lymphocyte proliferation from plasma cells [29].

Similarly, numerous studies have discussed the role of vitamin D in autoimmunity. In light of this information, it is assessed that vitamin D deficiency contributes to both stunted growth through nutritional effects and reduced bone mineral density through immunosuppressive effects in FMF patients. A common finding among these studies is the low levels of vitamin D in FMF patients, which supports the results observed in our research [30].

Given the immunosuppressive effect of vitamin D, it is evident that it influences disease severity. Furthermore, our study observed a significant incidence of growth retardation, approximately 16%, in FMF patients. This underscores the necessity of vitamin D replacement therapy in the management of FMF.

Studies have examined the impact of colchicine treatment on child development. It has been indicated that initiating colchicine therapy at an early stage in FMF can be beneficial [31]. Significant contributions of colchicine to height growth have been demonstrated [32]. Other studies have highlighted its positive effects on growth and its beneficial impacts on bone development [33,34].

There is no dispute regarding the positive effects of colchicine treatment on child development. However, the exact mechanism of this effect has not been fully elucidated. The frequent occurrence of short stature among FMF patients in our region can be attributed to delays in initiating treatment or interruptions in the treatment regimen by families. Our research identified that the educational level of parents is low, with the majority of families having only primary education. This suggests that the low educational level of parents could be a factor in treatment interruptions. Additionally, a low level of education may lead to reduced awareness of the disease, resulting in delays in diagnosis and initiation of treatment. Consequently, this manifests as a high incidence of developmental delay, as observed in our region.

Conclusion

The assessment and management of serum vitamin D levels are critical components in the comprehensive care of pediatric patients with FMF. Future research should aim to elucidate the precise mechanisms underlying vitamin D deficiency in FMF and establish standardized guidelines for optimal vitamin D supplementation in this vulnerable population. By addressing this modifiable risk factor, we can potentially improve disease outcomes and enhance the quality of life for pediatric patients afflicted with FMF.

In conclusion, the significant deficiency of serum vitamin D levels in pediatric FMF patients and its association with disease severity underscores the importance of regular monitoring and potential therapeutic intervention. Vitamin D supplementation could be a viable adjunctive therapy in the management of FMF, aimed at mitigating the inflammatory burden and improving overall patient outcomes. Further research is essential to substantiate these findings and to explore the underlying mechanisms linking vitamin D and FMF pathogenesis.

The study's limitations must be acknowledged. The cross-sectional design precludes establishing causality between vitamin D deficiency and FMF exacerbations. Longitudinal studies are warranted to ascertain whether vitamin D supplementation can effectively reduce the frequency and severity of FMF attacks. Additionally, the study population, being predominantly from a single geographic region, may limit the generalizability of the findings to broader populations with diverse genetic backgrounds and environmental exposures. In our study, participants' Height and Weight Percentile values were collected but were not included in the analysis and were presented only as demographic data. Additionally, analyzes that would add value to the study, such as mineral density and cytokines, are missing. These are other limitations in our study.

Declarations

Conflict of interest: None

Funding statement: None

Author Contributions: AIK, UO, MT: Protocol/project development, Data collection, Data analysis. Manuscript writing/editing. AIK, BAD & VA: Protocol/ project development, manuscript editing. AIK, UO, MT & VA: Protocol/project development, Data collection, Data analysis.

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