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ORIGINAL ARTICLE

The effect of vitamin D supplementation on attacks in PFAPA syndrome patients with low vitamin D levels

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Abstract

Background-aim To evaluate the effect of vitamin D supplementation on the frequency and duration of attacks in patients of PFAPA syndrome with low vitamin D levels.

Methods This retrospective study comprised PFAPA patients with vitamin D deficiency/insufficiency between 2018 and 2023. The frequency and duration of PFAPA attacks before and after vitamin D supplementation were noted.

Results Seventy-one patients were included. Of the 71 patients, 24 (33.8%) had vitamin D insufficiency, and 47 (66.2%) had vitamin D deficiency. In patients with vitamin D insufficiency, mean attack frequency and mean attack duration before vitamin D supplementation were 4.3 ± 1.9/year and 2.2 ± 1.6 days, respectively, while mean attack frequency and mean attack duration after vitamin D supplementation were 3.5 ± 2.7/year per year and 1.3 ± 0.9 days respectively ($p = 0.2$, $p = 0.2$, respectively). In patients with vitamin D deficiency, mean attack frequency and mean attack duration before vitamin D supplementation were 7.4 ± 2.1/year and 2.2 ± 1.6 days, respectively, while mean attack frequency and mean attack duration after vitamin D supplementation were 3.3 ± 2.4/year and 1.3 ± 0.9 days respectively ($p < 0.01$, $p = 0.04$, respectively). When the vitamin D level and the frequency of attacks were compared, the cut-off value of vitamin D was found to be 29.7 nmol/L.

Conclusions In PFAPA patients with low vitamin D levels, the frequency and duration of PFAPA attacks were reduced with vitamin D supplementation. Especially at vitamin D level cut-off > 29.7 nmol/L, the frequency of attacks reduced significantly.

Keywords Attack · Autoinflammatory disorders · Children · PFAPA syndrome · Vitamin D

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Introduction

The syndrome involving periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is the most common autoinflammatory disease in childhood [1]. It was first described by Marshall et al. in 1987 [2]. Before the age of 5 years, patients present with fever, pharyngitis, cervical lymphadenitis, and/or aphthous stomatitis lasting 3 to 7 days and recurring every 2 to 8 weeks [3, 4].

The etiology is not clearly known. The pathogenesis involves the dysregulation of different components of innate immunity such as monocytes, neutrophils, complement and pro-inflammatory cytokines, especially interleukin-1 beta (IL-1β), IL-18, and IL-6, and an inflammasome-mediated activation of the innate immune system [5–7].

Vitamin D has a major role in calcium homeostasis and bone formation. It has effects on the immune system including anti-inflammatory effects on antigen-presenting cells (APC) (monocytes, macrophages, dendritic cells), vitamin D receptor expression on B cells, the suppression of immunoglobulin E (IgE) secretion, and interferon gamma (IFN-γ) down regulation in natural killer (NK) cells. Vitamin D also increases the synthesis of IL-4, IL-5, and IL-10, inhibits the secretion of IL-12, IFN-c, and IL-2 and impedes T cell activation [8].

The aim of this study was to determine the effects of vitamin D treatment on the frequency and duration of attacks in patients with PFAPA syndrome with low vitamin D levels.

Material-methods

In this study, the medical file data of patients who were followed up with a diagnosis of PFAPA syndrome between January 2018 and January 2023 at Ankara Bilkent City Hospital were retrospectively reviewed.

Inclusion and exclusion criteria

Patients aged < 5 years who met the modified Marshall criteria [9] and Eurofever/PRINTO [3] classification criteria for PFAPA syndrome, had vitamin D levels below normal, and were followed up for at least 6 months after vitamin D treatment were included in the study.

Patients with symptom onset at > 5 years of age, comorbid diseases, or vitamin D metabolism disorders were excluded from the study. Additionally, due to health policies in Turkey, all patients under 1 year of age routinely receive vitamin D supplementation at a dose of 400 IU/day. Therefore, patients under the age of 1 year were excluded from the study to avoid the confounding effects of vitamin D supplementation.

Data collection and definitions

Demographic data (age, sex, family history, age of onset of symptoms, age of diagnosis) and clinical characteristics (fever, pharyngitis, lymphadenopathy, aphthous stomatitis, and other symptoms) were recorded. White blood cell (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), hemoglobin, platelets, acute phase reactants [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)], and vitamin D levels were also noted. 25-hydroxyvitamin D [25(OH)D] levels were measured in all patients using the enzyme immunoassay method. The 25(OH)D levels of the patients before and after vitamin D treatment were documented.

The normal ranges of parameters were taken as 5.4 – 13.8 103/μL for WBC, 1.5 – 8.5 103/μL for ANC, 2.2 – 8.5 103/μL for ALC, 10.7–13.9 g/dL for hemoglobin, 180–415 103/μL for platelets, 0–15 mm/h for ESR, 0–5 mg/L for CRP, and > 75 nmol/L for vitamin D.

The patients were divided into two groups according to their vitamin D levels. 25(OH)D levels of 50–75 nmol/L were defined as insufficiency, and levels of < 50 nmol/L were defined as deficiency [9].

The treatments given to the patients for PFAPA syndrome (colchicine, steroids, tonsillectomy, antipyretics) were recorded. Vitamin D3 (cholecalciferol) 2000 IU/day was given for 2–4 months [10].

Statistical analysis

Data were analyzed with the statistical package program IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), mean ± standard deviation, median, minimum value, and maximum value. Categorical variables were expressed as numbers and percentages. Kolmogorov–Simirnov/ Shapiro–Wilk test were used to determine whether the data distributed normally or non-normally. The Chi-square test was used to test differences in categorical variables between the two groups. Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off values of vitamin D to predict the association between vitamin D levels and attack frequency. All p-values < 0.05 were considered statistically significant.

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the ethics committee of Ankara Bilkent City Hospital (18.01.2023, E2-23-3178).

Results

During the study period, the medical file data of 342 patients who were followed up with a diagnosis of PFAPA syndrome were reviewed. Seventy-one patients who met the inclusion criteria were included in the study (Fig. 1). Of the patients, 39 (54.9%) were girls and 32 (45.1%) were boys. There were 42 patients (59.2%) aged 1–3 years and 29 patients (40.8%) aged 4–5 years. The median age at symptom onset was 17 months (range: 7–42), and the median age at diagnosis was 27 months (range: 14–54). Nineteen patients (26.4%) had a first-degree relative with a history of PFAPA syndrome in childhood.

All 71 patients had fever, 67 (94.4%) had pharyngitis, 41 (57.7%) had aphthous stomatitis, and 32 (45.1%) had lymphadenopathy.

During the attacks, the mean WBC was 9.7 ± 5.8 103/μL, their mean ANC was 6.8 ± 2.7 103/μL, their mean ALC was 2.5 ± 1.1 103/μL, their mean hemoglobin was 10.1 ± 2.6 g/dL, their mean platelets was 278.7 ± 138.9 103/μL, their mean CRP value was 59.4 ± 32.1 mg/L, and their mean ESR was 23.7 ± 17.9 mm/h.

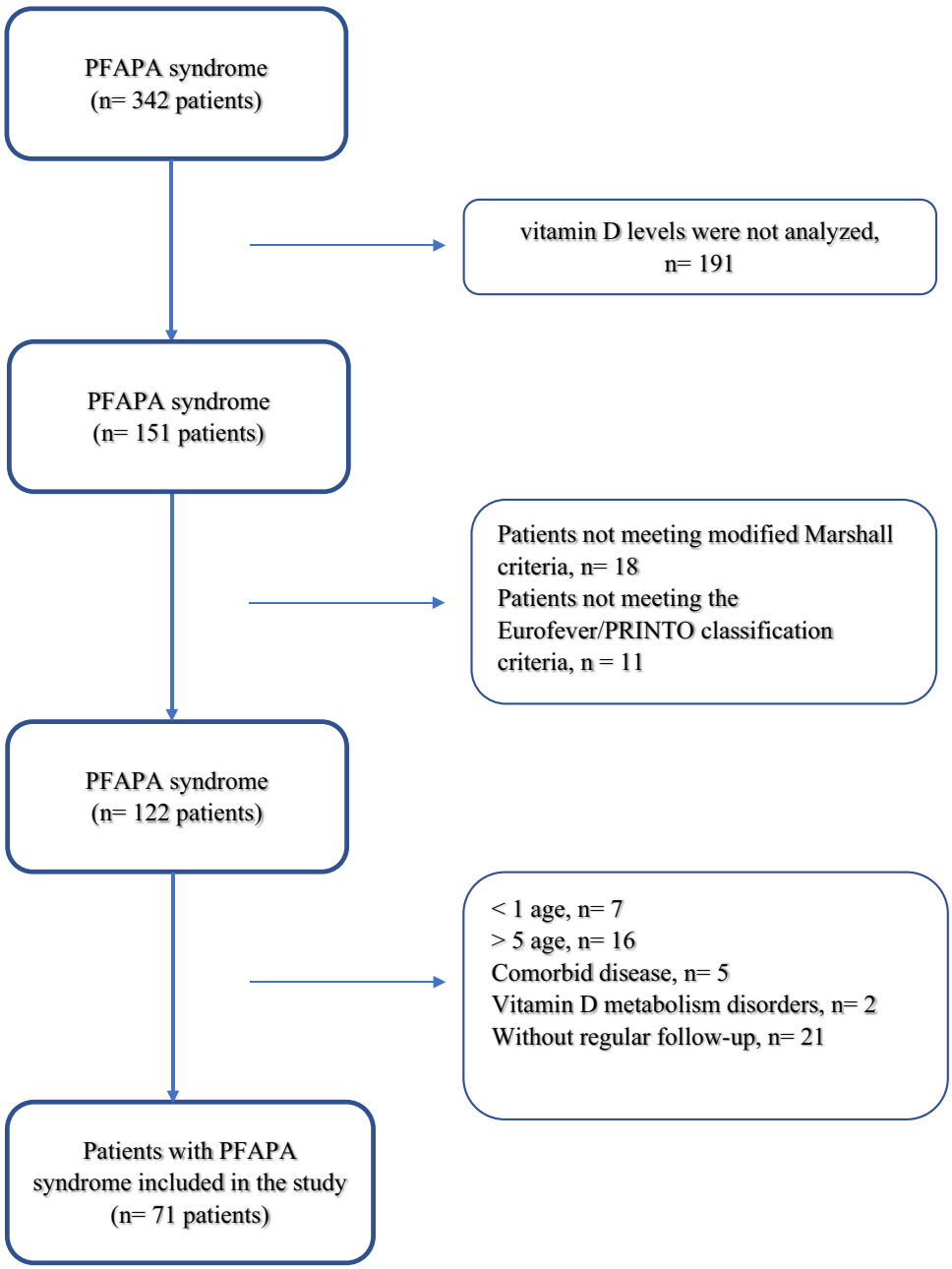

Fig. 1 Study inclusion flowchart

Fifty-one patients were given prophylactic colchicine. Three patients used steroids during their attacks. Seventeen patients were followed up without medication. Tonsillectomy was performed in 7 patients (5 patients who were followed up without medication and 2 patients who used colchicine).

Evaluation of vitamin D

The mean vitamin D level of the patients was 38.4 ± 16.3 nmol/L. Among 71 patients, 24 (33.8%) had vitamin D insufficiency, and 47 (66.2%) had vitamin D deficiency. Of the 24 patients (14 girls, 10 boys) with vitamin D deficiency, 11 were aged 1–3 years, and 13 were aged 4–5 years. Of the 47 patients (25 girls, 22 boys) with vitamin D deficiency, 31 were aged 1–3 years, and 16 were aged 4–5 years.

The mean duration of vitamin D supplementation was 2.8 ± 1.9 months in the vitamin D insufficiency group and 4.9 ± 2.7 months in the vitamin D deficiency group.

In the vitamin D insufficiency group, the mean frequency of attacks before vitamin D supplementation was 4.3 ± 1.9/year, and the mean duration of attacks was 2.3 ± 1.2 days, while the mean frequency of attacks after vitamin D supplementation was 3.5 ± 2.7/year, and the mean duration of attacks was 1.9 ± 1.1 days ($p = 0.2$, $p = 0.2$, respectively).

In the vitamin D deficiency group, the mean frequency of attacks before vitamin D supplementation was 7.4 ± 2.1/year, and the mean duration of attacks was 2.2 ± 1.6 days, while the mean frequency of attacks after vitamin D supplementation was 3.3 ± 2.4/year, and the mean duration of attacks was 1.3 ± 0.9 days ($p < 0.01$, $p = 0.04$, respectively). The results of the comparison of the vitamin D insufficiency and vitamin D deficiency groups are given in Table 1.

In the comparisons of the frequencies of attacks based on vitamin D levels, the ROC analysis of vitamin D yielded an area under the curve of 0.647, and the optimal cut-off value was found to be 29.7 nmol/L (Fig. 2).

In the comparisons of the vitamin D levels according to age groups, 42 patients aged 1–3 years had a mean vitamin D level of 31.6 ± 14.7 nmol/L, and 29 patients aged 4–5 years had a mean vitamin D level of 48.3 ± 19.4 nmol/L ($p = 0.03$). In the comparisons of the frequency and duration of attacks according to age groups, the frequency and duration of attacks were significantly higher in the patients aged 1–3 years before vitamin D supplementation ($p = 0.04$). After vitamin D supplementation, the frequency and duration of attacks decreased in both groups (Table 2).

Discussion

PFAPA syndrome is an autoinflammatory disease with recurrent and regular attacks that usually emerge before the age of 5 years [1]. Both innate immunity and adaptive immunity are considered to be involved in the pathogenesis of PFAPA syndrome, and vitamin D supplementation can be effective in controlling inflammation. In this study, 33.8% of 71 patients had vitamin D insufficiency, and 66.2% had vitamin D deficiency. In all patients, both the frequency and duration of attacks were significantly reduced with vitamin D supplementation. Especially the frequency of attacks decreased significantly at vitamin D levels of 30 nmol/L and above. Additionally, vitamin D deficiency rates and frequencies of attacks were found to be higher in the patients aged 1–3 years.

The immunological mechanisms underlying PFAPA syndrome are not clearly known. Increased neutrophil, monocyte, and macrophage counts during attacks indicate the activation of the innate immune system. IFN-γ is secreted from activated T cells and suppresses the synthesis of anti-inflammatory cytokines (IL-4, IL-10), which in turn increases monocyte/macrophage synthesis by feedback [11]. Additionally, there is an increase in T cell attractant chemokines accompanied by an activation and redistribution of T cells to local tissue, suggesting a subsequent adaptive immune response [7].

Vitamin D is a fat-soluble vitamin. Very few are obtained naturally from food, while the majority is synthesized from the skin. Vitamin D is involved in the regulation of calcium and phosphate balance to maintain healthy bone function [12]. Especially in recent years, its effects on the immune system have been investigated. Vitamin D modulates both the innate immune system through APCs and the adaptive immune system through antigens, T lymphocytes, and B lymphocytes via multiple pathways [13]. Based on these effects, the role of vitamin D in many autoimmune and autoinflammatory diseases has been researched [8, 14]. Few studies have focused on the effects of vitamin D in PFAPA syndrome [15–17]. Mahamid et al. showed that 22 PFAPA syndrome patients had significantly lower vitamin D levels compared to a healthy control group [15]. Stagi et al. reported a similar relationship and found a significant decrease in the frequency and duration of attacks after vitamin D supplementation [16]. In a recent study, it was reported that 38 of 50 PFAPA syndrome patients had low vitamin D levels, and serum 25(OH)D levels were associated with the occurrence of PFAPA attacks [17]. In our study, only PFAPA syndrome patients with low vitamin D levels were evaluated, and it was aimed to observe the effects of vitamin D supplementation on the outcomes. In fact, significant decreases in the frequency and duration of attacks were observed after vitamin D supplementation.

Table 1 Comparison of patients according to vitamin D level

	Vitamin D insufficiency, n = 24	Vitamin D deficiency, n = 47	*p*
Sex, n (%)			
Girl	14 (58.3%)	25 (53.2%)	0.61
Boy	10 (41.7%)	22 (46.8%)	0.3
Age, n (%)			
1–3	11 (45.8%)	31 (66%)	0.19
4–5	13 (54.2%)	16 (34%)	0.23
Duration of vitamin D supplementation, months, mean	2.8 ± 1.9	4.9 ± 2.7	**< 0.01**
Number of attacks, per year, mean (before vitamin D supplementation)	4.3 ± 1.9	7.4 ± 2.1	**< 0.01**
Number of attacks, per year, mean (after vitamin D supplementation)	3.5 ± 2.7	3.3 ± 2.4	0.82
Number of attacks, per year, mean (before/after vitamin D supplementation)	4.3 ± 1.9/ 3.5 ± 2.7	7.4 ± 2.1/ 3.3 ± 2.4	0.2[a] **0.01**[b]
Duration of attacks, days, mean (before vitamin D supplementation)	2.3 ± 1.2	2.2 ± 1.6	0.91
Duration of attacks, days, mean (after vitamin D supplementation)	1.9 ± 1.1	1.3 ± 0.9	0.74
Duration of attacks, days, mean (before/after vitamin D supplementation)	2.3 ± 1.2/ 1.9 ± 1.1	2.2 ± 1.6/ 1.3 ± 0.9	0.2[a] **0.04**[b]
Clinical findings n (%)			
Fever	24 (100%)	47 (100%)	1
Pharyngitis	22 (91.7%)	45 (95.7%)	0.63
Aphthous stomatitis	13 (54.2%)	28 (59.6%)	0.07
Lymphadenopathy	10 (41.7%)	22 (46.8%)	0.16
Laboratory findings, mean ± SD			
WBC, 10^3/μL	9.4 ± 5.2	10.1 ± 6.1	0.56
ANC, 10^3/μL	6.5 ± 2.9	7.1 ± 2.6	0.39
ALC, 10^3/μL	2.7 ± 1.3	2.4 ± 1	0.74
Hb, g/dL	10.2 ± 2.8	10.1 ± 2.5	0.92
Plt, 10^3/μL	284.1 ± 136.4	257.3 ± 142.9	0.72
CRP, mg/L	53.5 ± 34.2	61.6 ± 28.4	0.23
ESR, mm/h	25.1 ± 18	22.9 ± 17.8	0.48
Vitamin D, nmol/L	57.9 ± 6.6	29.7 ± 18.3	-
Treatment, n (%)			
Colchicine	17 (70.8%)	34 (72.3%)	0.62
Steroids	1 (4.2%)	2 (4.3%)	0.93
Follow up without medication	6 (25%)	11 (23.4%)	0.79
Tonsillectomy	2 (8.3%)	5 (10.6%)	0.56

The *p* values <0.05 were considered statistically significant

ALC Absolute lymphocyte count, *ANC* Absolute neutrophil count, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *Hb* Hemoglobin, *Plt* Platelet, *SD* Standard deviation, *WBC* White blood cell

[a]Comparison before and after vitamin D supplementation in patients with vitamin D insufficiency

[b]Comparison before and after vitamin D supplementation in patients with vitamin D deficiency

PFAPA syndrome usually developed between the ages of 1 and 4 years, and 90% of cases are diagnosed before the age of 5 years [18–20]. Rydenman et al. showed that the rate of onset of 336 PFAPA syndrome patients peaked at the age of 1 year and decreased in older ages [21]. In our study, the patients experienced the onset of their symptoms before the age of 3.5 years, and their age at diagnosis was before 4.5 years. Vitamin D deficiency is also common at these ages where PFAPA syndrome is frequently observed. In our study, vitamin D levels were found to be lower in the PFAPA syndrome patients aged 1–3 years. Vitamin D deficiency develops in children aged 1–3 years due to the inadequate dietary intake of vitamin D, lower levels of physical activity compared to older children, and less exposure to sunlight [22]. Therefore, several studies have recommended vitamin D supplementation for children in this age group [23, 24].

Low vitamin D levels are a risk factor for many diseases. For example, Milagres et al. reported that 32 ng/mL was the cut-off point for predicting cardiometabolic risk in children [25]. Sharifi et al. found a vitamin D cut-off level of 11.6 ng/mL for insulin resistance in 297 children [26]. In this study, the frequency and duration of PFAPA attacks were shown to increase among the patients with vitamin D levels below the normal level (75 nmol/L), and the increase was more significant below the cut-off of 30 nmol/L.

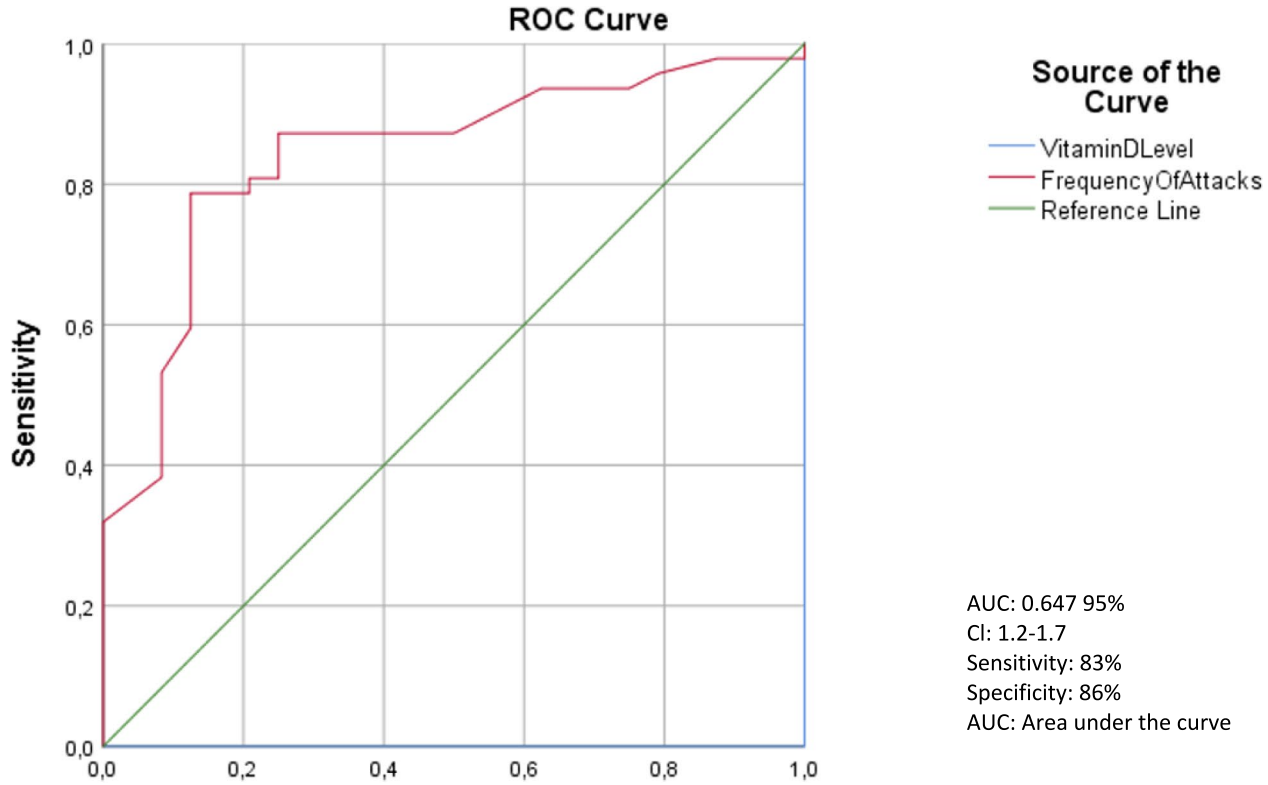

Fig. 2 ROC analysis of vitamin D for frequency of attacks in PFAPA

This study had some limitations. The main limitation was its retrospective design as a single-center study. Additionally, the relationship between treatment differences and vitamin D levels was not evaluated. To the best of our knowledge, this is the first study to compare the outcomes of PFAPA syndrome patients with low vitamin D levels before and after vitamin D supplementation. Moreover, a cut-off for vitamin D levels was determined for PFAPA syndrome patients. Defining a cut-off value for vitamin D levels in PFAPA syndrome cases and showing the target vitamin D levels will be useful and may shed light on future studies.

Table 2 Comparison of groups according to age groups

	1–3 years, n = 42	**4–5 years, n = 29**	***p***
Sex, n (%)			
Girl	23 (54.8%)	16 (55.2%)	0.89
Boy	19 (45.2%)	13 (44.8%)	0.91
Vitamin D, nmol/L	31.6 ± 14.7	48.3 ± 19.4	**0.03**
Duration of vitamin D supplementation, months, mean	4.1 ± 2.6	3.2 ± 2.4	0.08
Number of attacks, per year, mean (before vitamin D supplementation)	6.5 ± 2	4.8 ± 2.2	**0.04**
Number of attacks, per year, mean (after vitamin D supplementation)	3.4 ± 2.6	3.2 ± 2.3	0.81
Number of attacks, per year, mean (before/after vitamin D supplementation)	6.5 ± 2/ 3.4 ± 2.6	4.8 ± 2.2/ 3.2 ± 2.3	**< 0.01**[a] **0.05**[b]
Duration of attacks, days, mean (before vitamin D supplementation)	2.3 ± 1.4	2.2 ± 1.5	0.92
Duration of attacks, days, mean (after vitamin D supplementation)	1.9 ± 1.1	1.5 ± 0.7	0.87
Duration of attacks, days, mean (before/after vitamin D supplementation)	2.3 ± 1.4/ 1.9 ± 1.1	2.2 ± 1.5/ 1.5 ± 0.7	0.3[a] 0.1[b]

The *p* values <0.05 were considered statistically significant

[a]Comparison before and after vitamin D supplementation in patients aged 1–3 years

[b]Comparison before and after vitamin D supplementation in patients aged 4–5 years

Conclusion

Vitamin D levels should be checked in PFAPA syndrome patients who do not respond to treatment, and vitamin D supplementation should be given in patients with low vitamin D levels. The supplementation of vitamin D may reduce both the frequency and duration of attacks in PFAPA syndrome patients with vitamin D deficiency or insufficiency. Additionally, since PFAPA attacks are more common in young children, it may be beneficial to provide vitamin D supplementation, which is routinely given to patients under 1 year of age, for a longer period in PFAPA patients.

Author contribution All authors made substantial contributions to the conception or design of the work, have approved the final manuscript, and takes full responsibility for the manuscript. NO, BCA reviewed and revised the manuscript, NO, ZET, EC, VG and BCA contributed to the writing of the manuscript, NT, MS, CK, SC, MMK and MCP were responsible for data collection and analysis.

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Data availability Data can be provided upon request.

Declarations

Ethics approval The study was approved by the Ankara Bilkent City Hospital, ethics committee before the study. (Issue No: E2-23-3178).

Consent for publication This manuscript is not under simultaneous consideration by any other publication. All authors have approved the final manuscript and take full responsibility for the manuscript.

Conflict of interest The authors declare no competing interests.

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