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# VITAMIN D AND ITS CLINICAL SIGNIFICANCE IN JUVENILE IDIOPATHIC ARTHRITIS

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## Abstract

Vitamin D is known especially for its bone effects. Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in childhood. It was the aim of the present study to evaluate vitamin D status in patients with JIA and to assess the relationship between vitamin D levels and disease activity. A total of 44 patients with JIA, diagnosed according to the International League Against Rheumatism (ILAR) criteria and a control group (n=13), matched for age and sex, with no musculoskeletal complaints, were evaluated. Disease activity was assessed, X-ray was performed in clinically active joints, with disease duration more than 6 months and vitamin D level was measured. Significant lower values were obtained for vitamin D in JIA patients compared to the healthy controls, especially in patients

with systemic onset JIA and seropositive polyarticular arthritis. 66% of the children with arthritis were included in the group of vitamin D deficiency. Significant correlations were obtained between vitamin D level and the number of active joints, the number of joints with radiological evident lesions and disease duration, respectively. Vitamin D deficiency may be linked to disease severity and duration of the disease in JIA. The mostly affected JIA subtypes in vitamin D deficiency are the systemic and the seropositive polyarticular forms, and, therefore, these disorders should be routinely screened for vitamin D deficiency, and consequently treated. Recommendations for vitamin D supplementation in juvenile arthritis are needed.

## Introduction

Vitamin D was originally revealed as a vitamin involved in metabolism of calcium and phosphor. Two forms of vitamin D exist: vitamin D3 and vitamin D2, with very similar structure. The former is produced in the skin under the influence of UVB radiation (UVR); the latter is produced by UVR in a variety of plant materials and yeast (Bikle, 2009). The vitamin is hydroxylated to 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite of vitamin D. Although $1,25(OH)_2D$, synthesized in the kidney, portrays the biological active form of vitamin D, it is widely accepted that the measurement of circulating 25(OH)D provides better information with respect to patient's vitamin D status and allows its use in diagnosing hypovitaminosis.

Thousands of studies carried out to evaluate the role of vitamin D proved the presence of vitamin D receptors (VDR) in almost any cell and tissue of our body and its remote action on different organs. These remote effects and the fact that active vitamin D circulates in the blood brought to a new definition of vitamin D as a secosteroid hormone (Lin et al, 2004; Bikle, 2009).

Thereby, upon activation of VDRs, the biologically active metabolite of vitamin D: 25(OH)D exert a wide variety of biological responses, which influence immune modulation, cellular growth, proliferation and apoptosis (Lin et al, 2004; Toubi et al, 2010; Peelen et al, 2011; Agmon-Levin et al, 2012). Among the important target cells of vitamin D, in which VDRs were revealed, are the immune cells: lymphocytes, monocytes and dendritic cells, thus exposing the role of vitamin D as a positive immunomodulator (Van Etten et al, 2003; Holick, 2007; Agmon-Levin et al, 2012; Pelajo et al, 2010; Hewison, 2010). Through VDR expression, $1,25(OH)_2D$ exerts multiple effects on macrophages: it stimulates the differentiation of monocytic precursors in mature cells; enhances chemotaxis and phagocytosis; stimulates prostaglandin E2 (PGE2) production; decreases tumor necrosis factor (TNF) alpha and pro-inflammatory interleukins (IL-1, IL-6, IL-23) production; induces anti-inflammatory effect, interleukin (IL-10) secretion and the list can continue (Stoffels et al, 2006; Hewison, 2010; Alappat et al, 2010; Di Rosa et al, 2011). Vitamin D induces innate tolerance by multiple effects on dendritic cells: promotes tolerogenic dendritic cells; suppresses antigen presentation to T cells; regulates negatively dendritic cells differentiation; maturation and immunostimulatory capacity; decreases IL-6, IL-12 and IL-23 synthesis; impairs interferon-gamma (IFN-γ) production and many other actions (Van Etten et al, 2003; Holick, 2007; Pelajo et al, 2010; Hewison, 2010; Di Rosa et al, 2011).

Additionally, both humoral and cellular adaptive responses are affected by vitamin D (Agmon-Levin et al, 2012). Decreased proliferation and antibody production by B cells have been documented following exposure to vitamin D (Chen et al, 2007). The cellular response of vitamin D comprises a switch from Th1 to Th2 cytokines profile, ameliorating Th17 pathway via transcriptional modulation of IL-17, as well as induction of T regulatory cells (Treg) and immune tolerance (Peelen et al, 2011; Di Rosa et al, 2011; Cutolo, Pizzaroni et al, 2011; Cutolo, Plebani et al, 2011). Thereby, vitamin D has been accepted as one of the natural immune modulators and regulators of various immune mediated processes (Antico et al, 2012).

Juvenile idiopathic arthritis (JIA) is the most common rheumatic diseases of children. JIA is a broad term that describes a clinically heterogeneous group of arthritides of unknown cause, which begin before 16 years of age (Ravelli et al, 2007). Although the precise mechanism that leads to JIA remains unclear, it has been proposed that both innate and adaptive immunity are involved in pathogenesis of juvenile arthritis (Ravelli et al, 2007; Hahn et al, 2010). Oligoarthritis and polyarthritis are regarded as T helper 1 (Th1) cell-mediated inflammatory disorders, mainly based on the abundance of activated Th1 cells in the inflamed synovium and the pathogenic role of proinflammatory cytokines that are mainly produced by Th1 cell-stimulated monocytes (Harrington et al, 2005; Hahn et al, 2010). In contrast, there are no signs of lymphocyte-mediated, antigen-specific immune responses in individuals with systemic onset disease, and this disorder appears to be due to an uncontrolled activation of the innate immune system (Adams et al, 2005). Regardless of the differences in the underlying pathogenesis of the various types of JRA, pro-inflammatory cytokines are overproduced and are consistently related to the clinical manifestations in all types of JIA (Maeno et al, 2002; Adams et al, 2005; Pascual et al, 2005; Villanueva et al, 2005; De Jager et al, 2007).

## Objective

The main objectives of the study were to evaluate vitamin D status in patients with juvenile idiopathic arthritis (JIA) and to assess the correlation between vitamin D levels and disease activity.

## Methods

The study cohort consisted of 44 patients with juvenile idiopathic arthritis, admitted and assessed in First Pediatric Clinic, Timisoara, Romania. Diagnosis and classification were in concordance with International League Against Rheumatism (ILAR) criteria. A control group (n=13), matched for age and sex, with no musculoskeletal complaints, was evaluated as well. Assessment of study cohort included: 1) clinical examination with a 27 joint count for tender or swollen joint; 2) acute phase reactants determination (erythrocyte sedimentation rate=ESR, C- reactive protein=CRP); 3) patient or parent (according to age of child) assessment of well-being, measured on visual analogue scale (VAS), where 0=very well and 10= very poor; and 4) 25-hydroxyvitamin D levels in serum.

### *Measurement of disease activity*

Composite disease activity score (JADAS) was calculated as the linear sum of the scores of its four components: physician global assessment (VAS), parent or patient global assessment (VAS), active joint count (swollen joint count and tender joint count), normalized ESR (range 0 to 10). Normalized ESR values were obtained according to the following formula: [ESR (mm/hour) – 20] divided to 10. Before performing the calculation, ESR values < 20mm/hour were converted to 0 and ESR values > 120 mm/hour were converted to 120 (25).

### *25-hydroxyvitamin D measurement*

25(OH)D levels were measured in serum by enzyme-linked immunosorbent assay (ELISA) technique (from MDSS GmbH, Hannover, Germany). The assay performance was characterized by a lower detection limit of 5.6 nmol/L, and the mean of precision (intraassay of variation was 4.5-10.7%); with convert factor of 1 nmol/L=0.4ng/ml.

Interpretation of resulted 25(OH)D levels was according to the Endocrine Society's Clinical Guideline: "Evaluation, treatment, and prevention, of Vitamin D deficiency" (26). According to this guideline, vitamin D insufficiency is defined as serum levels of 25(OH)D included in a range between 21-29 ng/ml (52.5-72.5 nmol/l), and vitamin D deficit represents a situation with serum levels of 25(OH)D lower than 20ng/ml (50nmol/l).

### *Imagistic*

X-ray was performed just in clinically active joints, with disease duration more than 6 months, in order to evaluate the radiographic damage (erosions or joint space narrowing).

### *Statistical analysis*

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, version 17, IBM Company). We expressed the data as frequencies or means ± standard deviations, as appropriate. All statistical tests were performed for a 95% confidence interval (p value above .05 was considered statistically significant). We used the t-test for independent groups to assess differences of vitamin D levels indices across gender and JIA categories. We used the Spearman's test to evaluate correlations between vitamin D levels and other parameters. A rho value between -.3 and -.5 denotes a weak negative correlation, while a value between -.5 and -.7 a moderate one.

### *Ethics*

The study was approved by the ethics committees of the university. Informed consent was obtained from parents or guardians of all participating children.

## Results

### *Cohort description*

The JIA group included 26 girls and 18 boys, with median age of 12.4 ± 1.2 years. Control group included 8 girls and 5 boys, with median age of 12.1± 2.3 years. According to ILAR criteria, JIA cohort was divided in: 15 children with oligoarthritis, 14 patients with polyarthritis [4 seropositive (rheumatoid factor positive) and 10 seronegative], 3 cases with systemic onset arthritis and 11 children with enthesitis-related arthritis (ERA). Descriptive parameters of the cohort with juvenile arthritis are illustrated in table 1.

**Table 1.** Descriptive parameters of the cohort with juvenile arthritis (JIA)

| Type of JIA (number) | Median ESR (mm/1h) | Median CRP (mg/dl) | Mean disease duration (month) | Median JADAS |
|---|---|---|---|---|
| Systemic (3) | 49.8±12.7 | 12.2±5.7 | 8.6±2.5 | 19.8±3.5 |
| Oligo (15) | 27.5±11.9 | 7.35±4.3 | 7.9±3.2 | 6.3±2.9 |
| RF+ Poly (4) | 47.1±19.6 | 11.2±3.9 | 16.3±2.8 | 17.5±4 |
| RF- Poly (10) | 31.9±11.2 | 10.6±2.7 | 10.2±2.6 | 14.9±2.8 |
| ERA (11) | 20.1±7.1 | 4.8±1.3 | 14±4.2 | 11.7±4.7 |

ESR= erythrocyte sedimentation rate, CRP = C reactive protein, JADAS = Composite disease activity score, ERA = enthesitis-related arthritis, Oligo = oligoarthritis, Poly = polyarthritis, RF = rheumatoid factor

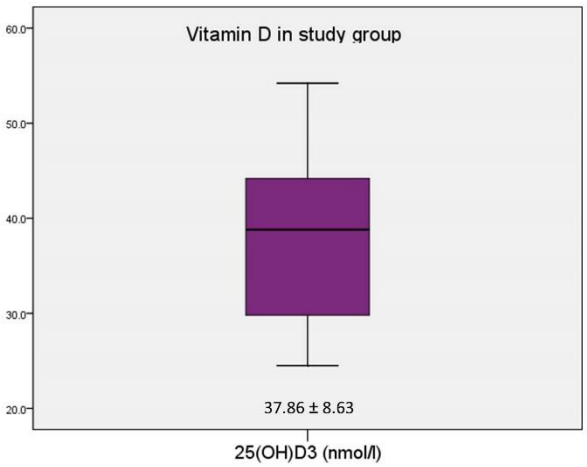



**Figure 1.** Vitamin D levels in children with JIA

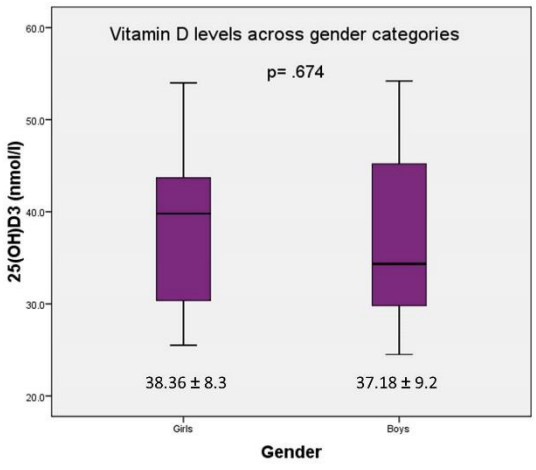
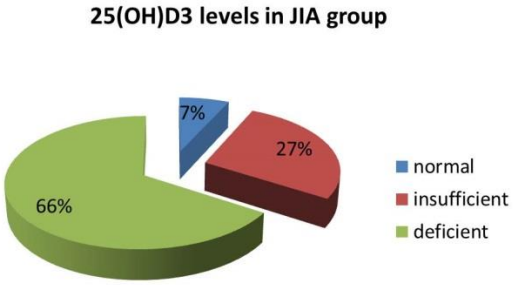



**Figure 2.** Vitamin D level and gender

### *Vitamin D measurement*

In JIA patients 25(OH)D median level was 37.86 ±8.63 nmol/L, corresponding to a deficient level of vitamin D (figure 1). Vitamin D levels evaluation across gender categories found no statistically significant differences between girls [with mean 25(OH)D value: 38.36±8.3] and boys [with median25(OH)D3 level: 37.18±9.2] (figure 2).

In 66% of the children with arthritis (n=29) levels of 25(OH)D were lower than 50 nmol/L, including them into the group of vitamin D deficiency (figure 2). 27% cases (n=12) had plasma levels of 25(OH)D3 ranged between 52.5 and 72.5 nmol/L, and just 3 patients (7%) presented normal vitamin D plasma level (figure 3). There were significant differences in vitamin D levels between JIA patients and controls, in which median 25(OH)D level was 75.2 ± 5.3 nmol/L (p=.0014). In 77% cases of the control group plasma levels of 25(OH)D were normal, and in 3 children (23%) vitamin D level was below 72.5nmol/l, representing an insufficient level (figure 4).



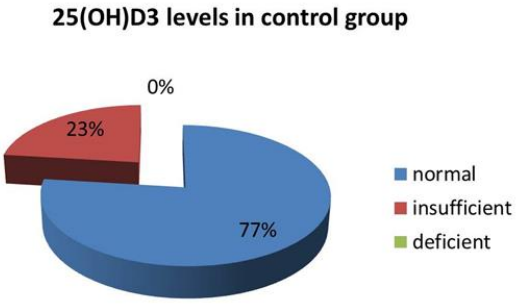




**Figure 3.** Vitamin D in children with JIA

**Figure 4.** Vitamin D in the control group

### *Vitamin D in subtypes of JIA*

We evaluated vitamin D level in the subtypes of JIA cohort (figure 5), and noticed that all cases with systemic onset JIA (n=3) and seropositive (RF positive) polyarticular arthritis (n=4) were deficient in vitamin D; while patients with ERA and oligoarthritis had almost

50% insufficient levels of 25(OH)D (figure 5).

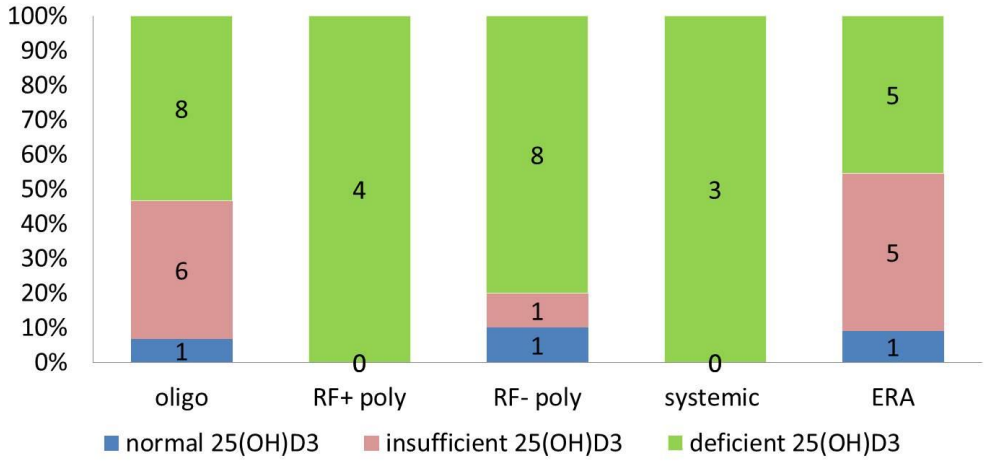



**Figure 5.** Vitamin D level in the subtypes of juvenile idiopathic arthritis cohort

We compared the mean levels of 25(OH)D in all JIA subtypes with control group, and found statistically significant differences (p=.000) (figure 6)

Statistically significant, but week negative correlations were found between 25(OH)D levels and the visual analogue scale (VAS) (rho= -.311, p=.042), and the number of active joints, respectively (rho=-.301, p=.049) (figure 7)

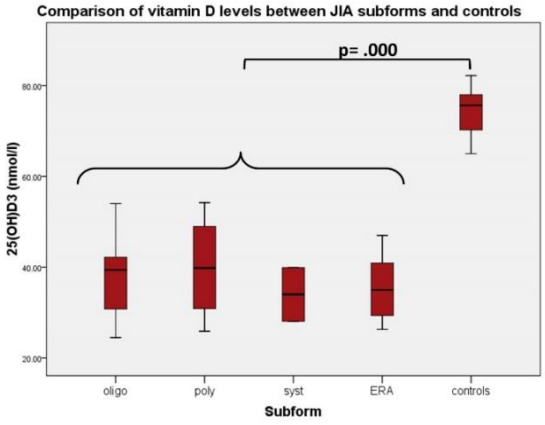



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**Figure 6.** Vitamin D level in the subtypes of juvenile idiopathic arthritis cohort and controls

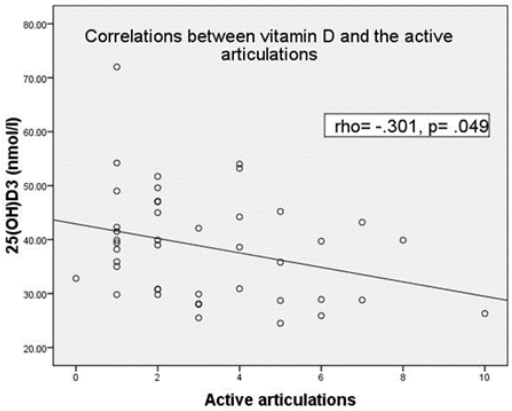


**Figure 7.** Correlation between vitamin D and number of active joints

Vitamin D levels were inversely and weekly correlated with the number of joints with radiological evident lesions, as well (rho=-.317 and p=.042) (figure 8).

Surprisingly, a moderate statistically significant negative correlation was found between vitamin D levels and disease duration (rho=-.485, p=.001) (figure 9).

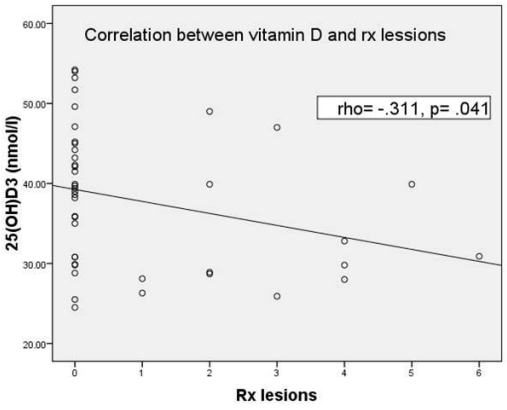


**Figure 8.** Correlation between vitamin D level and number of joints with radiological evident lesions

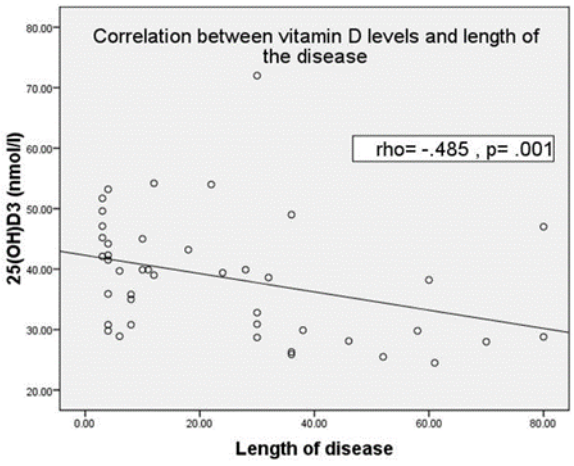


**Figure 9.** Correlation between vitamin D level and disease duration

## Discussions

In a large cohort (n=254) of pediatric patients with rheumatologic disorders, Pelajo and coworkers found that the average level of serum 25(OH)D was insufficient (Pelajo et al, 2010). The study concluded that patients with autoimmune disorders were more likely to be vitamin D deficient than patients with non-autoimmune conditions, and screening of serum 25(OH)D levels should be performed in pediatric patients with autoimmune disorders (Pelajo et al, 2010).

Another study of the same team, including 154 children with JIA, revealed vitamin D deficiency in 13% of the cases and insufficiency in 42% of the patients with chronic arthritis (Pelajo et al, 2012)

A recent systematic literature review (Nisar et al, 2013), revealed that three studies, reporting the prevalence of vitamin D deficiency in their cohorts, found that up to 82 % of children had insufficient levels. Our results are similar, even more dramatic: 66% of the children in our JIA group being vitamin D deficient, and 27% vitamin D insufficient, totalizing 93% of the cohort with lower than normal vitamin D levels.

Concerning vitamin D levels in JIA subtypes, a few studies reported lower levels of both 25(OH)D [mean 15.35, range 8.5-24.5 ng/ml] and $1,25(OH)_2D$ [ mean 22.89, range 5.6-50 pg/ml] in systemic JIA (Nisar et al, 2013). An older paper of Bianchi et al. showed that in the polyarticular and systemic groups, basal observation revealed decreased levels of 25(OH)D, significantly lower ($P< 0.01$) in comparison to the control and oligoarticular groups. They concluded that severe evolution of JIA has an influence on the bone mass, perhaps mediated by a decrease in active vitamin D metabolites (Bianchi et al, 1990). In our group as well, the polyarticular and systemic forms were the most deficient in vitamin D.

Furthermore, we found that in children with oligoarthritis and ERA as well, vitamin D levels were significantly lower in comparison with the control group.

There are very few studies which evaluate correlation between vitamin D level and disease activity in JIA. Pelajo et al. found that in univariate and multivariate analyses, 25(OH)D levels were not associated with JADAS score, neither with its individual components. However, in a subset analysis including all new-onset JIA patients (n = 27), there was a nonsignificant negative correlation between serum 25(OH)D levels and JADAS-27 (r = -0.29, P = 0.14) (Pelajo et al, 2012). Nevertheless, there are a lot of papers which reported a negative correlation between vitamin D levels and disease activity in rheumatoid arthritis (Cutolo et al, 2006; Rossini et al, 2010; Haque et al, 2010; Welsh et al, 2011; Kerr et al, 2011).

The most important limitation of our study is the low number of cases, which could explain both the controversial results and the lack of statistical significance. The paucity of papers which explore the role of vitamin D in juvenile arthritis permits no further discussions and considerations.

In rheumatoid arthritis, the combination of anti-rheumatic drugs with vitamin D supplementation has been suggested (Kim et al, 2012). Recently, vitamin D supplementation has been recommended for patients with rheumatoid arthritis for the prevention and treatment of osteoporosis as well as for its possible inhibitory effect on disease activity (Kim et al, 2012). There is no study concerning the effect of vitamin D supplementation on disease activity or outcome in juvenile arthritis.

A literature review concerning safety of vitamin D administration demonstrated that in most trials, reports of hypercalcemia and hypercalciuria were not associated with clinically relevant events, and there is little evidence from existing trials that vitamin D above current reference intakes is harmful (Cranney et al, 2007). The same paper showed a significant positive association comparable to an increase of 1 - 2 nmol/L in serum 25(OH)D for every 100 additional units of vitamin D. Cranney et al. highlighted the need for additional high-quality studies in infants, children, and diverse racial or ethnic groups (Cranney et al, 2007).

## Conclusion

Despite lower vitamin D levels in children with juvenile arthritis, interpretation is problematic as no agreed definition of vitamin D deficiency exists in this category. Standardization of vitamin D levels in the pediatric population, and specifically in juvenile arthritis is mandatory.

Vitamin D deficiency may be linked to disease severity in JIA, and could be correlated with duration of the disease. Further studies should be performed to confirm these results. The mostly affected JIA subtypes in vitamin D deficiency are the systemic and the seropositive polyarticular forms, therefore these disorders should be routinely screened for vitamin D deficiency, and consequently treated. Agreed recommendations for vitamin D supplementation in juvenile arthritis are needed.

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