Association between vitamin D deficiency and disease activity in juvenile idiopathic arthritis

Elif Çomak[1], Çağla Serpil Doğan[1], Arife Uslu-Gökçeoğlu[1], Halide Akbaş[2], Sabahat Özdem[2], Mustafa Koyun[1], Sema Akman[1]

[1]Division of Pediatric Nephrology and Rheumatology, Department of Pediatrics, and [2]Department of Biochemistry, Akdeniz University, Faculty of Medicine, Antalya, Turkey. E-mail: elif_comak@hotmail.com
Received: 4 March 2014, Revised: 26 June 2014, Accepted: 9 July 2014

SUMMARY: Çomak E, Doğan ÇS, Uslu-Gökçeoğlu A, Akbaş H, Özdem S, Koyun M, Akman S. Association between Vitamin D deficiency and disease activity in juvenile idiopathic arthritis. Turk J Pediatr 2014; 56: 626-631.

Vitamin D has been shown to have immunomodulatory and anti-inflammatory properties in addition to its well-established role in the maintenance of mineral homeostasis and bone health. The aims of this study were to evaluate vitamin D status in patients with juvenile idiopathic arthritis (JIA), and also to examine whether there is an association between serum levels of 25-hydroxyvitamin D [25(OH)D] and disease activity in JIA.

Children with JIA who had an outpatient visit between March and April 2011 were evaluated retrospectively. Clinical and laboratory findings and vitamin D levels were evaluated. Disease activity was calculated using JADAS-27. Serum vitamin D levels were measured using high-performance liquid chromatography (HPLC).

A total of 47 patients, 29 (61.7%) of them girls, with a mean age of 9.3±3.9 years and a median follow-up period of 28 months, were included in the study. The mean serum vitamin D level of all patients was 17.7±11.6 ng/ml. Vitamin D insufficiency (serum vitamin D: 15-20 ng/ml) and deficiency (serum vitamin D level <15 ng/ml) were found in 9 (19.1%) and 25 patients (53.2%), respectively. The vitamin D level was <20 ng/ml in 72.3% of the children. Only 13 patients (27.7%) were found to have adequate vitamin D levels (>20 ng/ml). There was a significant negative correlation between vitamin D levels and disease activity (p=0.01, r=-0,37). The mean JADAS-27 score was significantly higher in patients with 25(OH)D levels <15 ng/ml than in patients with 25(OH)D levels >15 ng/ml (p = 0.003).

We suggest that vitamin D deficiency may be a possible modifiable risk factor affecting disease activity in JIA.

Key words: vitamin D, deficiency, disease activity, juvenile idiopathic arthritis, children.

Vitamin D is critically important for the development, growth and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis[1].

While some vitamin D is obtained through diet, this hormone is obtained mostly through exposure of the skin to the sun. When bound to the active vitamin D ligand, the vitamin D receptor (VDR) acts as a transcription factor, regulating transcription of vitamin D-responsive genes. Thus, the VDR mediates the biological effects of vitamin D. The VDR is widely expressed in the cells of the immune system, including T cells and dendritic cells, suggesting that vitamin D plays an important role in immune regulation. Active vitamin D has a direct immunosuppressive effect on dendritic cells, reduces CD4 proliferation and differentiation into Th1 and Th17 and also increases production of Th2 and Treg cells[1-3].

The hypothesis that vitamin D has a relationship with autoimmune disorders was based on the observation that people living

near the equator had a decreased risk of developing common autoimmune diseases[4]. In addition, epidemiologic data indicate that vitamin D concentrations are low in individuals with autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel diseases and multiple sclerosis[5-7]. Moreover, it has been shown that children with autoimmune disorders, including juvenile idiopathic arthritis (JIA), are more likely to be vitamin D deficient than are controls[8,9].

In the last few years, the possible role of vitamin D in the pathogenesis, activity and treatment of RA has been suggested, based on the results and observations of clinical and laboratory studies[10]. However, there were conflicting results as to whether serum 25(OH)D levels were associated with disease activity. Some authors have found a relationship between 25(OH)D and disease activity in early inflammatory polyarthritis and RA[11-13], while others have found no association between 25(OH)D serum levels and disease activity in patients with RA and JIA[14,15].

Despite extensive evidence of vitamin D deficiency being associated with autoimmune rheumatologic disorders in adults, little information is available regarding children. The aims of this study were to evaluate vitamin D status in patients with JIA, and also to examine whether there is an association between serum levels of 25(OH)D and disease activity in JIA.

Material and Methods

Children with JIA who had an outpatient visit between March and April 2011 were evaluated retrospectively. Demographic data, disease duration, physical examination findings, disease activity, erythrocyte sedimentation rates and serum 25(OH)D levels were evaluated. Medications used for JIA treatment—calcium and vitamin D supplements, anti-TNF α agent (etanercept) and nonsteroidal anti-inflammatory drugs (NSAID), and disease-modifying antirheumatic drugs (DMARDs), including methotrexate, sulfasalazine, cyclosporine and prednisolone—and cumulative dosage of prednisolone (a dose of methylprednisolone was calculated as equivalent to prednisolone) were documented. The children were on stable doses of DMARDs, anti-TNF α agent and calcium and vitamin D supplements for 3 months prior to the assessment. Patients with a history of recent infection (within the previous 2 weeks) were excluded from the study since this could increase the inflammatory markers used to measure JIA disease activity. Body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). ILAR criteria were used for the classification of juvenile idiopathic arthritis[16].

Vitamin D deficiency was defined as a 25(OH) D serum level less than 15 ng/ml, vitamin D insufficiency as 25(OH)D levels of 15-20 ng/ml, and severe vitamin D deficiency as 25(OH) D levels of less than 5 ng/ml. Vitamin D levels greater than 20 ng/ml were considered sufficient[17].

Disease activity was evaluated using a previously validated score, JADAS-27[18]. This score includes the following 4 measures: physician global assessment of disease activity, measured on a 10-cm visual analog scale (VAS), where 0=no activity and 10=maximum activity; parent/patient global assessment of well-being, measured on a 10-cm VAS where 0=very well and 10=very poor; number of joints with active disease; and erythrocyte sedimentation rate (ESR). The JADAS-27 includes the following joints: cervical spine, elbows, wrists, metacarpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees and ankles. Each active joint's score is 1 point; the total ranges from 0 to 27. ESR is normalized to a score ranging from 0 to 10, according to the formula: (value in mm/hour - 20)/10, where values <20 mm/hour are converted to 0, and values >120 mm/hour are converted to 10. The JADAS is calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0–57, with higher scores representing greater disease activity.

Serum vitamin D levels were measured using a UV detector and high-performance liquid chromatography (HPLC) (LC 20AT, Shimadzu, Japan). An ImmuChrom brand kit (ImmuChrom GmbH, Tiergartenstr 7, Heppenheim Germany) was used. Intraassay coefficients of variation (CVs) were 2.6% (control value 22.6 μg/L) and 1.5% (control value 41.92 μg/L). The kit detection limit and the upper limit of linearity were found to be 2.32 μg/L and 500 μg/L, respectively.

Statistical Analysis

Statistical analysis comparing clinical data between the two groups [25(OH)D levels <20 ng/ml vs. >20 ng/ml and 25(OH)D levels <15 ng/ml vs. >15 ng/ml] consisted of unpaired t-tests for parametric data and Mann-Whitney U test analysis for nonparametric data, while analyses of a paired samples t-test for parametric data and the Wilcoxon signed-rank test for nonparametric data were used to compare different operation times within each group. To analyze correlations between JADAS-27 and 25(OH)D, the Pearson correlation coefficient was used. A multivariate linear regression analysis was performed to analyze the association between JADAS-27 and potential confounders. Analyses were performed using IBM SPSS Statistics, Version 19.0 (©Copyright IBM Corporation 2011, NY) software; a P value less than 0.05 was considered statistically significant.

Results

A total of 47 patients, 29 (61.7%) of them girls, with a mean age of 9.3±3.9 years and a median follow-up period of 28.96 months (range: 3-110 months), were included in the study. Patient characteristics, JIA subsets and treatment modalities are shown in Table I.

The mean serum 25(OH)D level of all patients was 17.7±11.6 ng/ml. Vitamin D insufficiency (serum vitamin D: 15-20 ng/ml) and deficiency (serum vitamin D level <15 ng/ml) were found in 9 (19.1%) and 25 patients (53.2%), respectively. Only 13 patients (27.7%) were found to have adequate vitamin D levels (>20 ng/ml) (Table II). The vitamin D level was <20 ng/ml in 72.3% children. No association was found between 25(OH)D levels and age, gender, JIA subtype, disease duration, JIA medications, inflammatory parameters (white blood cell counts, ESR and CRP), vitamin D supplements, use of prednisolone or BMI (all p>0.05). No difference was found between the serum 25(OH)D levels of the 11 children who used prednisolone and the levels of those who did not (17.9±6.4 and 17.7±1.3 ng/ml, p = 0.213). The cumulative dosage of prednisolone was 11.31±10.52 (1.22±31.51) g/m^2. There was no significant correlation between disease activity and cumulative dosage of prednisolone

Table I. Demographic Characteristics of Patients and Treatment Modalities

Parameters	
Age (mean±SD)	9.3±3.9 years
Male/Female, n (%)	18 (38.3%) / 29 (61.7%)
Disease duration, median (range)	28.9 months (3-110)
JIA subtype, n (%)	
Oligoarthritis	20 (42.6%)
Rheumatoid factor-negative polyarthritis	6 (12.8%)
Rheumatoid factor-positive polyarthritis	1 (2.1%)
Systemic-onset arthritis	13 (27.7%)
Enthesitis-related arthritis	6 (12.8%)
Psoriatic arthritis	1 (2.1%)
Medications, n (%)	
NSAID	6 (12.8%)
NSAID - Methotrexate	22 (46.8%)
NSAID - Methotrexate - Prednisolone	5 (10.6%)
NSAID - Sulfasalazine	2 (4.3%)
NSAID - Methotrexate - Etanercept	4 (8.5%)
NSAID - Methotrexate - Cyclosporin - Etanercept - Prednisolone	3 (6.4%)
NSAID - Methotrexate - Cyclosporin - Prednisolone	3 (6.4%)
Prednisolone (total), n (%)	11 (23.4%)
Cumulative dosage of prednisolone (g/m^2)	11.31±10.52 (1.22±31.51)
None, n (%)	2 (4.3%)

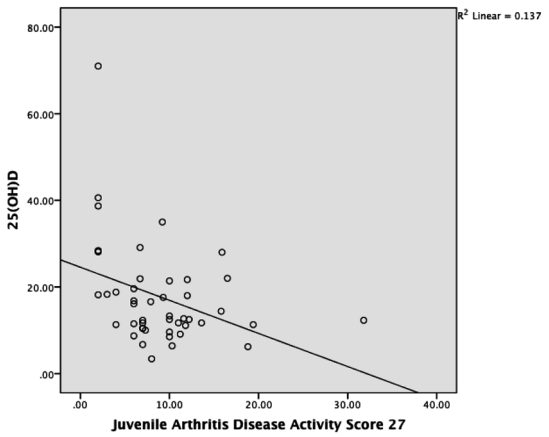

Fig. 1. The correlation between vitamin D and disease activity

(p=0.06, r=0.39). Twelve patients (25.5%) were using calcium and vitamin D supplements (equivalent to 600 mg elemental calcium and 400 IU vitamin D) at the time of the study. However, there was no significant difference between disease activity in and 25(OH)D levels of the children who used vitamin D supplements and those who did not (p=0.053 and p=0.021, respectively).

The median JADAS-27 score was found to be 8.9 (range: 2-31.8). There was a significant negative correlation between 25(OH)D levels and disease activity expressed as JADAS-27 (p=0.01, r=-0.37), as shown on Fig. 1. In the univariate linear regression analysis, serum 25(OH)D levels were associated with JADAS-27 (beta coefficient = -0.369; 95% CI = -0.312, 0.045; p=0.01). A similar association was found in multivariate linear regression analysis after adjusting for disease duration, use of vitamin D supplements, use of prednisolone and BMI (p=0.007 for vitamin D, p>0.05 for other parameters). In a subset analysis, we examined the correlation of serum 25(OH)D levels with JADAS-27 components. There was a significant negative correlation between 25(OH)D levels and physician VAS, parent VAS and joint count (p=0.001, p=0.001, p=0.02, respectively).

We found that the mean JADAS-27 score was higher in patients with 25(OH)D levels <20 ng/ml, but the result was not statistically significant [9.7±5.8 and 6.8±5.4 in patients with 25(OH)D levels <20 ng/ml and 25(OH) D levels >20 ng/ml (p=0.079), respectively]. On the other hand, the mean JADAS-27 scores were 10.9±5.7 and 6.6 ± 4.5 in patients with 25(OH)D levels <15 ng/ml and 25(OH)D levels >15 ng/ml (p=0.003), respectively, which was a statistically significant result.

Discussion

In this study, we demonstrated that serum 25(OH)D level was significantly correlated with disease activity in patients with JIA independent of age, gender, JIA subtype, disease duration, medications and BMI. In addition, these patients were found to have a high incidence of vitamin D deficiency and insufficiency.

There have been several studies reported in the literature investigating the relationship between vitamin D levels and disease activity in adult RA patients. In a prospective study carried out by Craig et al[19]., the vitamin D level was found to be inversely related with pain, joint swelling and disease activity in patients with newly diagnosed RA; this relation was not observed after 3 years. Heidari et al.[20] found a significant relationship between 25(OH)D deficiency and undifferentiated inflammatory arthritis (UIA), although such a relation was not observed in patients with RA. Similarly, Patel et al.[11] detected a relationship between serum 25(OH)D and disease activity in patients with early inflammatory polyarthritis. Rossini et al.[13] reported that disease activity and disability scores were inversely related to 25(OH)D levels. However, Braun-Moscovici

Table II. Serum 25(OH)D Levels of Patients

Serum 25(OH)D levels	n (%)
Severe deficiency (≤5 ng/ml)	0
Deficiency (<15 ng/ml)	25 (53.2)
Insufficiency (15–20 ng/ml)	9 (19.1)
Sufficiency (20–100 ng/ml)	13 (27.7)

et al.[14] found no relationship between disease activity and 25(OH)D levels in adult patients with inflammatory joint diseases. These findings indicate that patients with ongoing inflammatory processes may have lower vitamin D levels and that some relation exists between vitamin D levels and disease activity in patients with chronic inflammation.

Despite having similar characteristics, RA and JIA are different diseases. As far as we know, the study carried out by Pelajo et al.[15] is the only published report investigating the relation between disease activity and vitamin D in children with JIA. Researchers evaluated 154 children who were diagnosed with JIA and did not observe a relationship between 25(OH)D level and disease activity as evaluated by JADAS-27. However, a negative but not significant correlation was observed in newly diagnosed children. In that study, the mean vitamin D level was 29.2±9.2 ng/ml, while in 42% of the patients the level was 20–29 ng/ml. In our study, the vitamin D levels of the patients seem remarkably lower than those reported in the findings of the aforementioned study (the mean vitamin D level was 17.74±11.6 ng/ml; the vitamin D level of 72.3% of the patients was <20 ng/ml); in addition, we observed a significant negative correlation between disease activity and the 25(OH)D levels of the patients.

There is no consensus regarding optimal vitamin D levels. But research on adults has revealed that positive impacts of vitamin D start at levels >30 ng/ml, and that the best results are observed at 36-40 ng/ml[1]. However, the vitamin D levels that are required for the maintenance of immunological homeostasis have not yet been determined. In the present study, the mean JADAS-27 score was higher in patients with 25(OH)D levels <20 ng/ml, but this result was not statistically significant. When the children were grouped using a cutoff vitamin D level of 15 ng/ml, the mean JADAS-27 score was significantly higher in patients with 25(OH)D levels <15 ng/ml. These findings suggest that elevated serum 25(OH)D levels may lead to a decrease of disease activity in children with JIA. The threshold level at which vitamin D deficiency may affect JIA activity is not clear; therefore, further prospective studies including larger groups of children are needed to determine the cutoff levels of vitamin D with possible impacts on immunological homeostasis and disease activity. Also, there is no universal consensus on the definitions of vitamin D deficiency and insufficiency. Pelajo et al.[15] used vitamin D deficiency and insufficiency cutoffs of serum 25(OH)D ≤19 ng/ml and 20–29 ng/ml, respectively; vitamin D deficiency was detected in 13% and insufficiency in 42% of the patients in their study. In the present study, the levels recommended by Misra et al.[17] were used. Vitamin D insufficiency (serum vitamin D level = 15-20 ng/ml) and deficiency (serum vitamin D level <15 ng/ml) were found in 9 (19.1%) and 25 patients (53.2%), respectively. The Vitamin D level was <20 ng/ml in 72.3% of the patients. Given that our patients live in a sunny Mediterranean region, the vitamin D levels observed are surprisingly low. It is known that peak levels of vitamin D are observed in late summer, while the lowest values are observed at the beginning of spring[4]. Since the research was performed in the spring months, timing might be a reason for the high rates of vitamin D deficiency, but it is still difficult to explain these relatively low levels in the majority of patients on the basis of seasonal effects alone.

A number of drugs alter vitamin D levels. Anticonvulsants, corticosteroids, cimetidine, antituberculosis agents, theophylline and orlistat decrease vitamin D levels, while thiazide diuretics may increase them[4,21]. It is also known that steroid treatment decreases serum vitamin D levels. Out of 47 patients, 11 were on maintanance steroid treatment for induction or continuation of remission, which might also be a reason for low vitamin D levels. However, a significant difference was not observed between the 25(OH)D levels of patients receiving and not receiving steroid treatment. It may be due to the fact that the patients receiving steroid treatment were also taking vitamin D supplements.

BMI has been proven to be inversely related to 25(OH)D levels; this was attributed to the sequestration of fat-soluble vitamin D in adipose tissue[22]. However, there was no significant relation between 25(OH)D levels and BMI in the present study.

This retrospective study has some limitations. 1) Nutritional status, vitamin D content of the

diet, daily topical sunscreen utilization, daily physical activities and degree of exposure to sun could not be assessed. This was considered to be the most significant limitation of the study, as these are important confounding factors affecting the level of vitamin D. 2) The small number of patients in the present study made it difficult to assess the possible effects of JIA medications, vitamin D supplements and prednisolone use on vitamin D levels. 3) A control group was lacking. The results would be more definitive if we had been able to measure vitamin D levels in healthy children. 4) Another limitation of the present study is that we did not evaluate the relation between 25(OH)D levels and disease activity in JIA subgroups due to the very small size of each subgroup.

The findings of the current study suggest that vitamin D deficiency may have an effect on the disease activity of JIA. Considering the impact of vitamin D on the modulation of the immune system, clinicians should be aware of vitamin D deficiencies in this group of patients. Reversal of vitamin D deficiency may also positively affect disease activity. However, prospective comprehensive studies are needed to further investigate the relationship between vitamin D and disease activity.

REFERENCES

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266-281.
2. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis, and inflammatory bowel disease. Prog Biophys Mol Biol 2006; 92: 60-64.
3. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab 2009; 94: 26-34.
4. Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. Autoimmun Rev 2010; 9: 507-510.
5. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Vitamin D status, parathyroid hormone and bone mineral density in patients with inflammatory bowel disease. Scand J Gastroenterol 2002; 37: 192-199.
6. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS. Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 2006; 5: 114-117.
7. Orbach H, Zandman-Goddard G, Amital H, et al. Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. Ann N Y Acad Sci 2007; 1109: 385-400.
8. Comak E, Dogan CS, Uslu Gokceoglu A, et al. Juvenil idiyopatik artrit tanılı çocuklarda D vitamini düzeyleri. Çocuk Sağlığı ve Hastalıkları Dergisi 2012; 55: 191-196.
9. Pelajo CF, Lopez-Benitez JM, Miller LC. 25-hydroxyvitamin D levels and vitamin D deficiency in children with rheumatologic disorders and controls. J Rheumatol 2011; 38: 2000-2004.
10. Cantorna MT, Mahon BD. Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp Biol Med (Maywood) 2004; 229: 1136-1142.
11. Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 2007; 56: 2143-2149.
12. Cutolo M, Otsa K, Laas K, et al. Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe. Clin Exp Rheumatol 2006; 24: 702-704.
13. Rossini M, Maddali Bongi S, La Montagna G, et al. Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants and associations with disease activity and disability. Arthritis Res Ther 2010; 12: R216.
14. Braun-Moscovici Y, Toledano K, Markovits D, Rozin A, Nahir AM, Balbir-Gurman A. Vitamin D level: is it related to disease activity in inflammatory joint disease? Rheumatol Int 2011; 31: 493-499.
15. Pelajo CF, Lopez-Benitez JM, Kent DM, Price LL, Miller LC, Dawson-Hughes B. 25-hydroxyvitamin D levels and juvenile idiopathic arthritis: Is there an association with disease activity? Rheumatol Int 2012; 32: 3923-3929.
16. Petty RE, Southwood TR, Baum J, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998; 25: 1991-1994.
17. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008; 122: 398-417.
18. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009; 61: 658-666.
19. Craig SM, Yu F, Curtis JR, et al. Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. J Rheumatol 2010; 37: 275-281.
20. Heidari B, Hajian-Tilaki K, Heidari P. The status of serum vitamin D in patients with rheumatoid arthritis and undifferentiated inflammatory arthritis compared with controls. Rheumatol Int 2012; 32: 991-995.
21. Cannell JJ, Hollis BW, Zasloff M, Heaney RP. Diagnosis and treatment of vitamin D deficiency. Expert Opin Pharmacother 2008; 9: 107-118.
22. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000; 72: 690-693.