Determinants of Vitamin D Levels in Children, Adolescents, and Young Adults with Juvenile Idiopathic Arthritis

Stefano Stagi, Federico Bertini, Loredana Cavalli, Marco Matucci-Cerinic, Maria L. Brandi, and Fernanda Falcini

ABSTRACT. Objective. Deficiency of 25-hydroxyvitamin D [25(OH)D] is reported to be common in patients with rheumatoid arthritis (RA); data in patients with juvenile idiopathic arthritis (JIA) are inconsistent. We assessed serum 25(OH)D in children, adolescents and young adults with JIA, in order to identify the risk factors for vitamin D deficiency in patients with JIA.

Methods. We evaluated 152 patients with JIA: 115 female, 37 male, mean age 16.2 ± 7.4 yrs; evaluated by onset type, 96 had oligoarticular, 35 polyarticular, 7 systemic, and 14 enthesitis-related arthritis (ERA). Patients were compared with a control group matched for sex and age. All patients and controls underwent laboratory tests of plasma 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, and bone alkaline phosphatase levels, and dual-energy x-ray absorptiometry examination.

Results. Patients with JIA showed significantly reduced 25(OH)D levels compared to controls (p < 0.001), even divided into subtypes (oligoarticular, p < 0.05; polyarticular, p < 0.005; systemic, p < 0.001; ERA, p < 0.005). Patients with active disease and/or frequent relapses had significantly reduced 25(OH)D levels compared to patients with no active disease and no frequent flares (p < 0.005, respectively). Nevertheless, JIA patients had significantly higher PTH levels compared to controls (p < 0.0001). JIA patients with 25(OH)D deficiency showed a significantly lower bone mineral apparent density than those with normal 25(OH)D levels (p < 0.001).

Conclusion. JIA patients have reduced 25(OH)D and higher PTH values. This may explain at least in part why JIA patients, despite more effective current drugs, do not achieve bone-normal condition over time. JIA patients with more severe disease could require higher supplementation of vitamin D to maintain normal 25(OH)D serum levels. Longterm studies are needed to investigate the relationship between serum 25(OH)D levels and disease activity in JIA. (First Release Aug 1 2014; J Rheumatol 2014;41:1884–92; doi:10.3899/jrheum131421)

Key Indexing Terms:
BONE MINERAL DENSITY         JUVENILE IDIOPATHIC ARTHRITIS         OSTEOPOROSIS
25 OH VITAMIN D         PARATHYROID HORMONE

Vitamin D status varies significantly among different countries in Europe, the Middle East, and Asia1,2 due to differences in exposure to sunshine, dietary intake of vitamin D, and use of supplements2. Many factors affect the cutaneous synthesis of vitamin D including age, season, latitude, time of day, skin pigmentation, amount of skin exposed, and use of sunscreen2.

Vitamin D status is defined according to the serum concentration of 25-hydroxyvitamin D [25(OH)D]. On the basis of many studies, the prevalence of 25(OH)D deficiency varies from 2% to 30% in adults2,3, although 1 Italian study found that insufficiency or deficiency of 25(OH)D was common4. However, an evaluation of satisfactory levels of vitamin D in healthy children has not yet been reported by adequate studies.

Adequate 25(OH)D status is important because vitamin D deficiency may lead to factors that contribute to fracture risk, including secondary hyperparathyroidism and osteoporomalacia2,5. Two studies conducted with adolescent girls suggested that lower vitamin D status correlated with
smaller gains in lumbar spine area bone mineral density (BMD).7,8

Recently, 25(OH)D deficiency and/or insufficiency have been associated with loss of muscle mass8 and muscle weakness9. In addition, studies have suggested that 25(OH)D deficiency may be a risk factor for the development of autoimmune and other chronic diseases6,10. Emerging data have led to the hypothesis that vitamin D may play an important role in immunity regulation11,12,13. In vitro studies have detected that vitamin D metabolites may modulate T cell proliferation and dendritic cell function14,15, upregulation of the antiinflammatory cytokine interleukin 10 (IL-10), and downregulation of proinflammatory cytokines, and may enhance production of regulatory T cells (T-reg)11. It has been hypothesized that vitamin D may inhibit Th1 and Th17 cells — found in excess in juvenile idiopathic arthritis (JIA) — via several pathways including reduction of IL-6 production, inhibition of proliferation and differentiation of B cells, and the increase of apoptosis12.

JIA is the most common form of chronic arthritis in children, with a prevalence of up to 160/100,00016. The etiology is unknown, although immune dysfunction is pivotal in its pathogenesis17. In patients with rheumatoid arthritis (RA), 25(OH)D deficiency is reported to be common17,18,19,20,21,22,23,24,25, and low 25(OH)D levels are associated with disease activity19,23,24,25,26,27, physical disability21, and cardiometabolic intermediates22. However, data for the pediatric population are scarce, and the role of vitamin D in the development and perpetuation of JIA is not clear26.

The purpose of this study was to assess serum 25(OH)D levels in children, adolescents, and young adults with JIA, and to identify the risk factors for vitamin D deficiency in this population.

MATERIALS AND METHODS

We cross-sectionally evaluated 152 children, adolescents, and young adults that fulfilled the criteria for JIA27, who were consecutively recruited from the Rheumatology Unit of the Transition Clinic at the University of Florence between May 2010 and September 2013. The Hospital Ethics Committee approved the study protocol, which was in accord with the Declaration of Helsinki. Written informed consent was obtained from all patients and controls and/or their parents/guardians.

Study design. For each patient, clinical and demographic data including type and onset of JIA, age at diagnosis, disease duration, disease course, flares, therapies, height, pubertal stage, weight, body mass index (BMI), and family history for osteoporosis were recorded from medical charts. All children underwent examination and laboratory tests to measure plasma 25(OH)D levels, serum calcium and phosphate, bone-specific alkaline phosphatase (BSAP), and parathyroid hormone (PTH). All underwent dual-energy x-ray absorptiometry (DEXA) examination of the lumbar spine on the day of the blood and clinical examinations. Onset of JIA was defined as the date on which arthritis and/or systemic disease) or being in clinical remission for at least 6 consecutive months exhibiting one or more of the following: absence of morning stiffness, no active arthritis, ESR < 20 mm/h, and independent of medication in systemic and polyarticular patients. Relapse was defined according to the preliminary definition of disease flare in JIA30.

Type of treatment. For this study we considered the following therapies: nonsteroidal antiinflammatory drugs (NSAID), sulfasalazine, systemic and/or intraarticular corticosteroids, methotrexate, and tumor necrosis factor-α (TNF-α)-blocking agents30.

For all drugs, in particular corticosteroids, the period of administration was also obtained from the outpatient clinic and hospital records for both the time of diagnosis and at DEXA evaluation. Also noted was the number of intraarticular glucocorticoid injections and the interval between the injection and DEXA assessment. Systemic corticosteroid dosage was converted to a common steroid equivalence.

Healthy controls. The control group included 188 healthy age- and sex-matched subjects (142 female, 46 male; median age 15.3 yrs, range 8.3–24.2 yrs) seen at our units for noninflammatory musculoskeletal complaints. Data from a subsection of these groups were also previously reported30.

Onset of JIA was defined as the date on which arthritis and/or systemic features were documented by a pediatric rheumatologist30. The disease subtype and the active JIA assessment were defined as described30.

No participant had a history of recent travel to warmer or sunnier areas prior to enrolment. Exclusion criteria for the recruitment of both JIA patients and controls, on the basis of medical history and questionnaires for osteoporosis risk factors, included the following: bone metabolic diseases, hyper/hypoparathyroidism or other skeletal diseases, hyper/hypothyroidism, chronic renal failure, cancer, pregnancy, lactation, mal-absorptive disorders, type 1 or 2 diabetes (DM), obesity (defined as BMI > 95th percentile for age and sex), and use of bone-related specific drugs. In particular, we excluded for hormonal therapies (aromatase inhibitors, gonadotropin-releasing hormone agonists, medroxyprogesterone acetate, thyroid replacement therapy) and central nervous system agents (anticonvulsants, antipsychotic agents).

To avoid seasonal variations, although solar winter is typically defined as the period between November and February, we defined winter as the period from November to May and summer as June to October because human insolation exposure to UVB radiation is negligible between November and April30.

Vitamin D values were categorized as being desirable (or sufficient) between 30 and 40 ng/ml (75–100 nmol/l), insufficient between 20 and 30 ng/ml (50–75 nmol/l), deficient between 10 and 20 ng/ml, and severely deficient < 10 ng/ml.

Parents completed a standardized interview record that included religion, country of birth, birth weight, type of feeding during the first year (breast, formula milk, or mixed), mother’s use of vitamin supplementation during pregnancy, child’s use of vitamin D supplementation, and daily intake of cow milk (categorized as more or less than 200 ml/day).

Dietary intakes of calcium and vitamin D were assessed by interview during the visit. Depending on the age of the child, the parent or guardian and the child were interviewed with the use of food models, portion booklets, or serving containers to assist in estimating serving size. Nutrient analyses were obtained from the Food Composition Database for Epidemiological Studies in Italy (Banca Dati di Composizione degli Alimenti per Studi Epidemiologici in Italia; BDA). For subjects reporting the use of dietary supplements, the possible calcium and vitamin D contents from supplement sources were evaluated during the study interview.

Clinical assessment of disease activity. As described30, clinical disease activity was determined on the basis of the core set criteria for JIA, such as medical history and physical examination — in particular, the number of active joints, number of joints with limited range of motion, physician’s global assessment of disease activity, parent’s/patient’s assessment of overall well-being [visual analog scale as part of the Childhood Health Assessment Questionnaire (CHAQ), and functional ability (disability as measured in 8 domains by the CHAQ)].

The leucocyte count (cells/µl), absolute neutrophil count (cells/µl), red blood cell count (cells/µl), platelet count (cells/µl), erythrocyte sedimentation rate (ESR; mm/h), and C-reactive protein (CRP; mg/dl) were measured as serum markers of inflammation30.

Patients were categorized as having active disease (joint active or sign of systemic disease) or being in clinical remission for at least 6 consecutive months exhibiting one or more of the following: absence of morning stiffness, no active arthritis, ESR < 20 mm/h, and independent of medication in systemic and polyarticular patients. Relapse was defined according to the preliminary definition of disease flare in JIA30.

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The patient population consisted of 115 females and 37 males with a mean age of 16.2 ± 7.4 years. In regard to JIA onset, 96 subjects were oligoarticular type, 35 polyarticular, 7 systemic, and 14 enthesitis-related arthritis (ERA). Demographic and disease-specific characteristics of all study participants (patients with and without vitamin D deficiency and controls) are shown in Table 1.

Analyzing the different medication exposure at study entry, 30.9% of patients with JIA had received NSAID. Methotrexate and TNF-α-blocking agents were prescribed to 41.4% and 25.6% of patients, respectively, while 29.6% were given sulfasalazine. High-dose systemic or oral glucocorticoids were administered only to patients with onset of systemic JIA (p < 0.001). In the other subgroups, the dose administered was low, and the groups did not exhibit statistical differences. Thirty-six percent of patients had undergone glucocorticoid therapy during the year prior to DEXA assessment.

At the start of the study, disease duration was found to be 129.5 ± 11.1 months (range 6–420 mo), and was not significantly different between females (137.9 ± 90.3 mo) and males (116.1 ± 110.7 mo; p = nonsignificant), or among the different subtypes of arthritis (Table 1). Ninety-three patients (61.2%) did not have disease activity, whereas 59 [38.8%; 44 female (28.9%), 16 male (10.5%)] had disease activity. Among JIA patients with active disease, there was no significant difference among the different subtypes (Table 1).

No statistically significant differences were found between JIA patients and controls regarding history of fractures, calcium intake, standard deviation score (SDS) for height, and SDS for BMI (Table 1).

Evaluation periods varied seasonally: 79 patients (52.0%) were evaluated during the winter period and 73 (48.0%) in the summer. There were no statistical differences with controls (53% evaluated during the winter period and 47% in the summer). There were no statistical differences among the number of JIA females and males studied in the different seasons.

Evaluating 25(OH)D levels, 87.5% of patients with JIA showed reduced (< 30 ng/ml) 25(OH)D values, without statistical differences in comparison to controls (80.2%, p = NS). However, we observed a statistical difference regarding the frequency of reduced 25(OH)D levels among oligoarticular [81/96 patients (84.3%)], polyarticular [30/35 patients (88.6%)], ERA [11/14 (78.6%)], and systemic [7/7 (100%)] onset (respectively, 84.3%, 88.6%, and 78.6% vs 100%; p < 0.005) between controls and systemic (80.2% vs 100%; p < 0.0001) and polyarticular onset (88.6% vs 80.2%; p < 0.0001).

Evaluating 25(OH)D levels in particular, 19 subjects (12.5% vs 14.4% of controls; p = NS) had insufficient levels, 58 (38.2% vs 41.3% of controls; p = NS) had deficient levels, and 14 (9.2% vs 5.1% of controls; p = NS) had a severe deficiency (Figure 1).
Table 1. Demographic, clinical, and serological data in patients with juvenile idiopathic arthritis (JIA) and controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>JIA</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects (F:M)</td>
<td>152 (115:37)</td>
<td>188 (142:46)</td>
<td>—</td>
</tr>
<tr>
<td>Age, mean yrs ± SD</td>
<td>16.2 ± 7.4</td>
<td>15.4 ± 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Height, SDS</td>
<td>–0.5 ± 1.0</td>
<td>–0.1 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, SDS</td>
<td>–0.3 ± 0.7</td>
<td>0.0 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pubertal development</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td>47 (36:11)</td>
<td>61 (48:13)</td>
<td>NS</td>
</tr>
<tr>
<td>Pubertal</td>
<td>56 (42:14)</td>
<td>68 (52:16)</td>
<td>NS</td>
</tr>
<tr>
<td>Postpubertal</td>
<td>49 (37:12)</td>
<td>59 (42:17)</td>
<td>NS</td>
</tr>
<tr>
<td>Dietary intake of vitamin D, IU/day</td>
<td>139 ± 43</td>
<td>147 ± 48</td>
<td>—</td>
</tr>
<tr>
<td>Dietary intake of calcium, mg/day</td>
<td>828 ± 231</td>
<td>852 ± 187</td>
<td>—</td>
</tr>
<tr>
<td>JIA onset type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>96 (63.2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Polyarticular</td>
<td>35 (23.0)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>7 (4.6)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Enthesitis-related</td>
<td>14 (9.2)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, mean yrs ± SD</td>
<td>5.3 ± 3.6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>4.8 ± 2.6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Polyarticular</td>
<td>5.9 ± 3.5</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>4.2 ± 3.3</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Enthesitis-related</td>
<td>8.0 ± 2.2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Disease duration, mean mo ± SD</td>
<td>129.5 ± 11.1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>CHAQ-DI</td>
<td>0.71 ± 0.58</td>
<td>0.71 ± 0.58</td>
<td>—</td>
</tr>
<tr>
<td>BMC, g</td>
<td>48.77 ± 21.56</td>
<td>56.98 ± 16.82</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>BMAD L2–L4, SDS</td>
<td>–0.72 ± 0.83***</td>
<td>0.20 ± 0.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>25(OH) vitamin D, ng/ml</td>
<td>21.8 ± 8.2**</td>
<td>29.8 ± 11.2</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/ml</td>
<td>46.8 ± 26.9******</td>
<td>25.1 ± 11.0</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**p < 0.005; ***p < 0.001. Data are means ± SD. SDS: standard deviation score; CHAQ-DI: Childhood Health Assessment Questionnaire Disability Index; BMC: bone mineral content; BMAD: bone mineral apparent density.

Figure 1. 25(OH) vitamin D levels (ng/ml) in all patients with juvenile idiopathic arthritis (JIA), subtypes, and controls. JIA vs controls: *p < 0.05; **p < 0.005; ***p < 0.001. Systemic vs other JIA subtypes: ^p < 0.05; ^^p < 0.005. Oligoarticular vs polyarticular: °p < 0.05.
However, patients with JIA showed significantly reduced 25(OH)D levels compared to controls (21.8 ± 8.2 vs 29.8 ± 11.2 ng/ml, respectively; p < 0.001). In particular, patients with oligoarticular onset showed a 25(OH)D level of 23.7 ± 8.3 ng/ml (p < 0.05); polyarticular 20.8 ± 6.1 ng/ml (p < 0.005); systemic 15.5 ± 7.3 ng/ml (p < 0.001); and ERA 21.3 ± 7.0 ng/ml (p < 0.005), with significant differences among JIA subtypes (Figure 1). The 25(OH)D levels were not different comparing males (20.7 ± 8.8 ng/ml) and females (22.1 ± 7.3; p = NS), children (22.4 ± 7.9 ng/ml), adolescents (21.6 ± 7.5 ng/ml; p = NS), and young adults (21.0 ± 7.7 ng/ml; p = NS).

These differences were constant during the different periods of the year. Patients with JIA showed reduced 25(OH)D levels compared to controls both in winter (16.7 ± 7.4 vs 26.5 ± 8.5 ng/ml; p < 0.005) and in summer (28.9 ± 11.3 vs 37.8 ± 13.5 ng/ml; p < 0.005), with 25(OH)D in the range of severe deficiency only in winter.

Patients with JIA and active disease showed significantly reduced 25(OH)D levels (17.1 ± 9.4 ng/ml) compared to non-active patients (24.9 ± 11.3 ng/ml; p < 0.005; Figure 2). Also, patients with frequent relapses (> 2/yr) had significantly reduced 25(OH)D levels (16.7 ± 10.0 ng/ml) compared to those with infrequent relapses (25.2 ± 10.6 ng/ml; p < 0.005). In these patients, the differences in the different subgroups regarding the cumulative dose of corticosteroids were greater, but were not statistically significant.

In patients with JIA, total calcium levels were normal (2.38 ± 0.15 vs 2.49 ± 0.13 mmol/l; p = NS) compared to controls, as were phosphate levels (2.10 ± 0.14 vs 2.13 ± 0.16 mmol/l; p = NS). In contrast, JIA patients exhibited significantly higher BSAP levels (100.9 ± 32.1 vs 54.9 ± 19.3 U/l; p < 0.001) in comparison to controls. These differences were also present when JIA patients were divided into children (143.1 ± 36.7 vs 82.3 ± 17.4 U/l; p < 0.001), adolescents (127.1 ± 26.3 vs 60.8 ± 15.1 U/l; p < 0.001), and young adults (53.4 ± 13.2 vs 32.3 ± 10.7 U/l; p < 0.001).

In addition, a significantly higher percentage of JIA patients showed hyperparathyroidism compared to controls (25.6% vs 2.2%, respectively; p < 0.001). However, 20.8% of oligoarticular (20/96), 34.3% of polyarticular (12/35), 57.1% of systemic (4/7), and 28.6% of ERA (4/14) patients showed higher percentages of hyperparathyroidism, with statistical differences among the different subtypes (oligoarticular vs polyarticular, p < 0.005; oligoarticular vs systemic, p < 0.0001; polyarticular vs systemic, p < 0.0001; and ERA vs systemic, p < 0.0001).

Analyzing PTH levels, JIA patients showed significantly higher values compared to controls (46.8 ± 26.9 vs 25.1 ± 11.0 pg/ml; p < 0.0001; Figure 3). PTH levels were higher in winter (54.8 ± 36.5 pg/ml) than in summer (34.2 ± 21.5 pg/ml; p < 0.005); however, this difference was not significant in controls (28.3 ± 14.4 vs 23.5 ± 10.6 pg/ml; p = NS).

Finally, JIA patients had reduced SDS values for spine BMAD compared to controls (–0.72 ± 0.83 vs 0.20 ± 0.26, respectively; p < 0.001). Interestingly, when we evaluated BMAD values on the basis of the presence of deficiency in 25(OH)D levels, we observed a significant difference (deficiency, –1.78 ± 0.77 vs non-deficient, –0.49 ± 0.85; p < 0.001; Figure 4).

Evaluating the correlations among 25(OH)D and age, sex, seasons, BMAD, PTH, BMI, height, disease activity, disease duration, and treatments, we noted that 25(OH)D levels correlated with PTH (r = –0.49, p < 0.005), calcium (r = –0.36, p < 0.005), phosphorus (r = 0.47, p < 0.005), BSAP (r = –0.45, p < 0.005), BMI (r = –0.51, p < 0.005),
protein (r = –0.26, p < 0.05), relapses (r = –0.39, p = 0.008), ESR (r = –0.41, p < 0.001), and CRP levels (r = –0.53, p < 0.001).

Multivariate linear regression analyses showed that serum 25-OHD concentration was negatively associated with BMI (β = 0.25, p = 0.009) and disease activity (β = 0.28, p = 0.019).

DISCUSSION

Our results confirm that vitamin D insufficiency and deficiency are common in patients with JIA, and provide data on 25(OH)D status in a significant sample of children, adolescents, and young adults with chronic arthritis. Whereas the percentages of JIA patients with reduced 25(OH)D levels were comparable with those of the healthy controls, patients with JIA showed significantly lower 25(OH)D levels with respect to controls; this result demonstrates that vitamin D deficiency was more important in these patients.

However, our data show that JIA patients have different

Figure 3. Parathyroid hormone levels (pg/ml) in patients with juvenile idiopathic arthritis (JIA) and controls. **p < 0.005.

Figure 4. Bone mineral apparent density (BMAD) in patients with juvenile idiopathic arthritis (JIA) with and without 25(OH)D deficiency. ***p < 0.001.
vitamin D levels in relation to articular involvement and onset subtypes, with more reduced 25(OH)D levels in polyarticular and systemic onset compared to oligoarticular and ERA. These results may suggest a reduced immunomodulatory role of hypovitaminosis D in patients with more severe disease. For example, patients with multiple sclerosis have lower serum 25(OH)D levels during relapses. However, other authors provide data on significantly decreased levels of vitamin D with significant negative associations with biomarkers of inflammation in type 1 DM compared with control subjects.

It has also been suggested that vitamin D is involved in immunoregulatory activities, and the vitamin D receptor has been detected in immune system cells, such as mononuclear, dendritic, antigen-presenting cells, and activated T-B lymphocytes. In addition, activated dendritic cells produce vitamin D.

Hence, higher dosage of 25(OH)D supplementation in patients with more severe JIA subtypes, active disease, or frequent relapses could be considered.

In adults it has been reported that vitamin D intake was inversely associated with the risk of rheumatoid arthritis (RA). However, in patients with RA vitamin D levels may also affect the outcome of treatment, with findings of clinical improvement due to a possible immunomodulating role in RA patients treated with vitamin D. Further, the role of hypovitaminosis D in the etiopathogenesis of JIA and the role of vitamin D supplementation in the management of JIA remain unclear.

In children, a metaanalysis of 14 reports quoting 25(OH)D levels showed a mean vitamin D level of 24.56 ng/ml (range 11.5–56.4 ng/ml) in a total of 529 children. Nevertheless, PTH levels were reported in 9 studies with a mean of 25.1 pg/ml (range 5.3–44 pg/ml) in a total of 425 children. Our data from a population of patients with JIA support the results of previous studies, in which 50%–69% of JIA patients had unsatisfactory 25(OH)D levels, and stressed the problem of 25(OH)D deficiency, because more than 80% of our patients showed 25(OH)D levels < 30 ng/ml.

It is interesting that we observed significant inverse correlations between vitamin D levels and disease activity, and that patients with active disease presented significantly lower 25(OH)D levels than those without active disease. This result confirms the data from Cutolo, et al on an adult sample with RA, but contrasts with findings from Pelajo, et al who reported no association between serum 25(OH)D levels and disease activity.

Nevertheless, our results suggest the hypothesis that reduced 25(OH) vitamin D levels that correlated with the more important inflammation of polyarticular and systemic onset disease may represent the consequence of the reduced immunomodulatory role of hypovitaminosis D, and reflect the local or systemic immunoregulatory role of vitamin D in the disease; as well they may explain reduced levels in JIA patients with many flares versus patients without relapses. Conversely, lower levels of 25(OH) vitamin D could be a consequence rather than the cause of high disease activity, as for example the reduced sun exposure in patients with active disease.

In our study, the season strongly influenced vitamin D status, and mimicked the differences of 25(OH)D levels in controls. This may result from reduced skin production of vitamin D during winter, and less sunlight exposure of the children with JIA. However, we found no difference in the prevalence of 25(OH)D in the range of deficiencies among children, adolescents, and young adults with JIA. Thus, prescription of vitamin D supplementation should represent a primary tool for these patients, in particular in those with the more severe onset type or disease course.

Our analysis found a relatively high prevalence of vitamin D deficiency in patients with JIA; however, the results depend upon the definition for the “normal range” of vitamin D. No universally accepted or evidence-based range exists in children, and even among adult cohorts there is controversy whether previously accepted “normal” levels of vitamin D are in fact sufficient. PTH levels may represent a useful indicator of 25(OH)D adequacy in JIA patients or other subjects with reduced vitamin D levels, even if we do not have an optimal range of PTH for children and adolescents. Indeed, in contrast to other authors, we detected, without therapeutic intervention, increased values of PTH. Bianchi, et al also reported such increased values, and they hypothesized the role of sufficient vitamin D status in maintaining a normal bone metabolism.

Our results suggest that vitamin D should be supplemented in patients with low levels, at least maintain homeostasis. A consensus about how and when it should be administered, and whether this would have any influence on disease outcome, is recommended.

The notable results from our study are that children, adolescents, and young adults with normal vitamin D levels have significantly higher BMAD compared to patients with vitamin D insufficiency or deficiency. We previously reported that JIA patients have low bone mass and, after an initial increase due to the appropriate therapy, do not achieve the normal condition over time despite use of current more effective drugs, and still have high risk of osteoporosis in early adulthood. Thus, factors such as normalization of vitamin D levels might play a role in increasing the peak bone mass and thus ameliorate the BMAD, in particular, in patients with more severe forms of arthritis.

Patients with JIA displayed reduced serum 25(OH)D levels, associated with higher PTH values, compared to controls. The Z-score for BMAD was significantly different depending on 25(OH)D level. This result may be explained, at least in part, because patients with JIA do not achieve
normal bone conditions over time despite use of the current more effective drugs. Therefore, patients with severe disease subtypes, such as those with polyarticular and systemic onset, could require higher levels of supplementation to maintain normal 25(OH)D levels. Longterm studies are needed to determine the relationship between serum 25(OH)D levels and disease activity.

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