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 Asia[1,2] due to differences in exposure to sunshine, dietary intake of vitamin D, and use of supplements[2]. 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 sunscreen[2].

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 adults[2,3], although 1 Italian study found that insufficiency or deficiency of 25(OH)D was common[4]. 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 osteoporomalacia[2,5]. Two studies conducted with adolescent girls suggested that lower vitamin D status correlated with

From the Health Sciences Department, University of Florence, Anna Meyer Children's University Hospital, Florence; Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence, Florence; and Department of Internal Medicine, Endocrinology Unit, University of Florence, Florence, Italy.

S. Stagi, MD, Health Sciences Department, University of Florence, Anna Meyer Children's University Hospital; F. Bertini, MD, Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence; L. Cavalli, MD, Department of Internal Medicine, Endocrinology Unit, University of Florence; M. Matucci-Cerinic, MD, Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence; M.L. Brandi, MD, Department of Internal Medicine, Endocrinology Unit, University of Florence; F. Falcini, MD, Department of BioMedicine, Section of Rheumatology, Transition Clinic, University of Florence.

Address correspondence to Prof. F. Falcini, Department of Internal Medicine, Section of Rheumatology, Transition Clinic, Viale Pieraccini 18, 50139 Florence, Italy. E-mail: falcini@unifi.it

Accepted for publication May 29, 2014.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

smaller gains in lumbar spine area bone mineral density (BMD)[6,7].

Recently, 25(OH)D deficiency and/or insufficiency have been associated with loss of muscle mass[8] and muscle weakness[9]. In addition, studies have suggested that 25(OH)D deficiency may be a risk factor for the development of autoimmune and other chronic diseases[5,10]. Emerging data have led to the hypothesis that vitamin D may play an important role in immunity regulation[11,12,13]. *In vitro* studies have detected that vitamin D metabolites may modulate T cell proliferation and dendritic cell function[14,15], 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 apoptosis[12].

JIA is the most common form of chronic arthritis in children, with a prevalence of up to 160/100,000[16]. The etiology is unknown, although immune dysfunction is pivotal in its pathogenesis[11]. In patients with rheumatoid arthritis (RA), 25(OH)D deficiency is reported to be common[17,18,19,20,21,22,23,24,25], and low 25(OH)D levels are associated with disease activity[19,23,24,25,26,27], physical disability[21], and cardiometabolic intermediates[22]. However, data for the pediatric population are scarce, and the role of vitamin D in the development and perpetuation of JIA is not clear[28].

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 JIA[29], 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 features were documented by a pediatric rheumatologist[29]. The disease subtype and the active JIA assessment were defined as described[30].

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 April[31].

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[5].

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 described[30], 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 leukocyte 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 inflammation[30].

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 JIA[30].

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 agents[30].

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 equivalency.

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 reported[30].

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

DEXA scans. BMD was measured at the lumbar spine by DEXA using a strict protocol with the same instrument (Delphi-A 4500 System). All BMD results were expressed as g/cm^2 or BMD Z-scores. Average BMD values for L2-L4 were used for calculations.

Because the software for DEXA instruments does not take into account the actual bone volume — strictly related to body size (weight and height) — the formula from Kröger, *et al* was used for estimation of the respective volumetric density (bone mineral apparent density; BMAD), as reported[30,32,33]:

$$BMAD = BMD_{L2\text{-}L4} \times [4/(\pi \times width)], \text{ expressed in g/cm}^3.$$

The Kröger model was validated by *in vivo* volumetric data obtained from magnetic resonance imaging of the lumbar vertebrae[34]. Patients' BMAD data were also expressed as Z-scores. All BMD measurements were performed by the same operator. The intraobserver coefficient of variation was 1.0%.

Study and laboratory methods. Height was measured using a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg. BMI was calculated as weight divided by height squared (kg/m^2). Age-related reference values of height and BMI were obtained from a wide sample of Italian children[34]. Height and BMI were normalized for chronological age by conversion to standard deviation scores.

Pubertal staging was performed and followed the criteria of Tanner and Whitehouse[35]. Pubertal onset was assessed and compared between the healthy population and patients ith JIA, as described[30].

Blood samples were obtained from each study participant after an overnight fast. Hemoglobin levels, white blood cell count, platelet count, ESR, CRP, serum creatinine, and plasma concentrations of calcium and phosphate were measured using standard tests.

The serum level of BSAP was measured by immunoassay (Metra Biosystems) with a sensitivity of 0.7 U/l and a coefficient of variation of 3.9%–5.8%.

Serum 25(OH)D was determined by chemiluminiscence enzyme-labeled immunometric assays using an Immulite 2000 systems analyzer (Siemens). The intra- and interassay coefficients of variation (CV) were < 5% and < 10%, respectively. This technique differs from tandem mass spectrometry, which is widely used for this type of analysis because immunoassays have given erroneous results at low levels[36].

PTH levels were also determined by chemiluminescence enzyme-labeled immunometric assays using an Immulite 2000 analyzer. The intra- and interassay CV were < 8% and < 10%, respectively.

Statistical analysis. Statistical analyses were performed using SPSSX. The characteristics of the study population were described through frequency distributions for categorical variables and through means and SD, medians, and ranges for continuous variables, depending on whether the data were normally distributed. Differences between patient groups and controls were assessed using the Student t-test and Mann-Whitney U-test, depending on the distribution of the variable. The chi-square test and Fisher's exact test were used, as appropriate, to examine associations between dichotomous variables. Intergroup comparisons for variables were conducted using analysis of variance (ANOVA) or repeated-measures analysis of covariance (ANCOVA), as appropriate.

Spearman and/or Pearson correlation test was used to determine correlation coefficients. A multiple stepwise regression was performed to investigate factors associated with insufficient vitamin D status, after adjustment for potential confounders (age, sex, disease duration, cumulative corticosteroid dose, vitamin D intake, BMI). Covariates that were found to be not significant at the 0.05 level were removed from the regression model by stepwise elimination. P values < 0.05 were considered statistically significant.

RESULTS

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 sufficient vitamin D levels, 61 (40.1% vs 38.2% 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).

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

Table 1. Demographic, clinical, and serological data in patients with juvenile idiopathic arthritis (JIA) and controls.

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

**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.

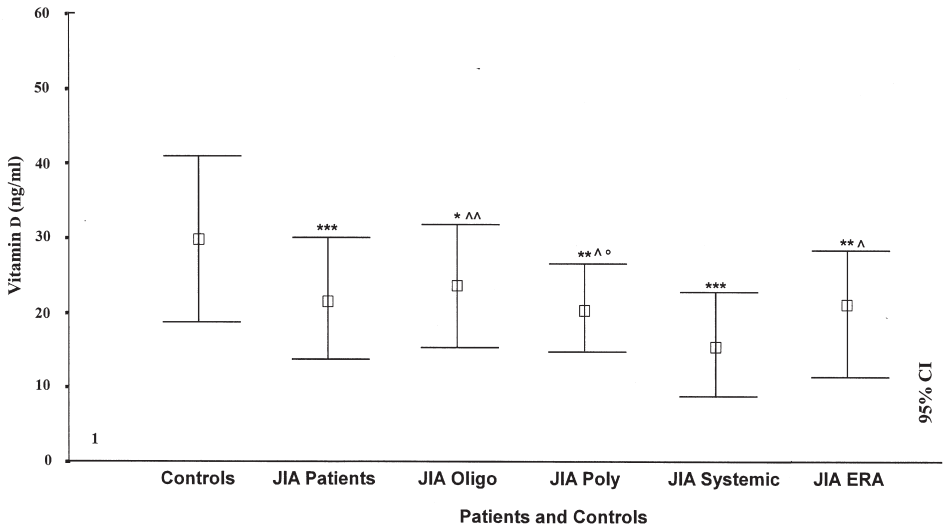

Figure 1. 25(OH) vitamin D levels (ng/ml) in all patients with juvenile idiopathic arthritis (JIA), subtypes, and controls. JIA vs controls: *p < 0.05; **p < 0.005; ***p < 0.001. Systemic vs other JIA subtypes: ^p < 0.05; ^^p < 0.005. Oligoarticular vs polyarticular: °p < 0.05.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

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 without frequent 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 not 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 ($r = –0.51$, $p < 0.005$),

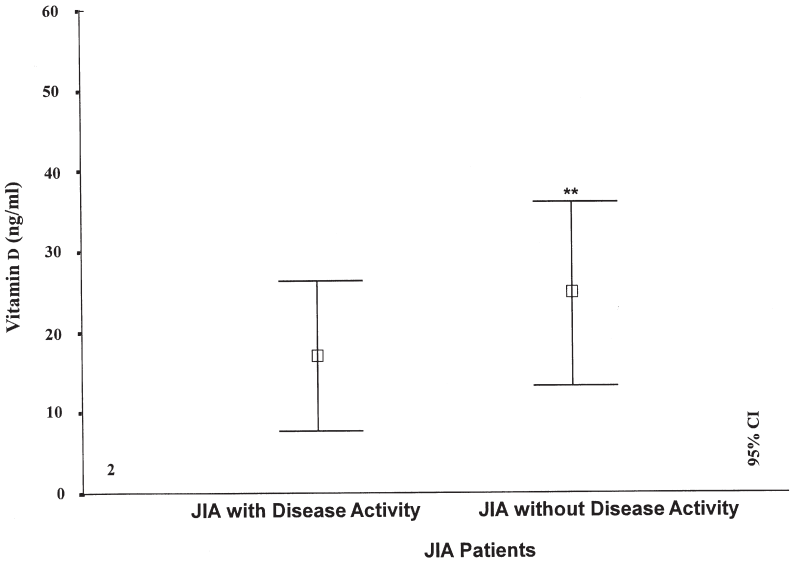

Figure 2. 25(OH) vitamin D levels (ng/ml) in patients with juvenile idiopathic arthritis (JIA) with and without disease activity. *$p < 0.05$; **$p < 0.005$; ***$p < 0.001$.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

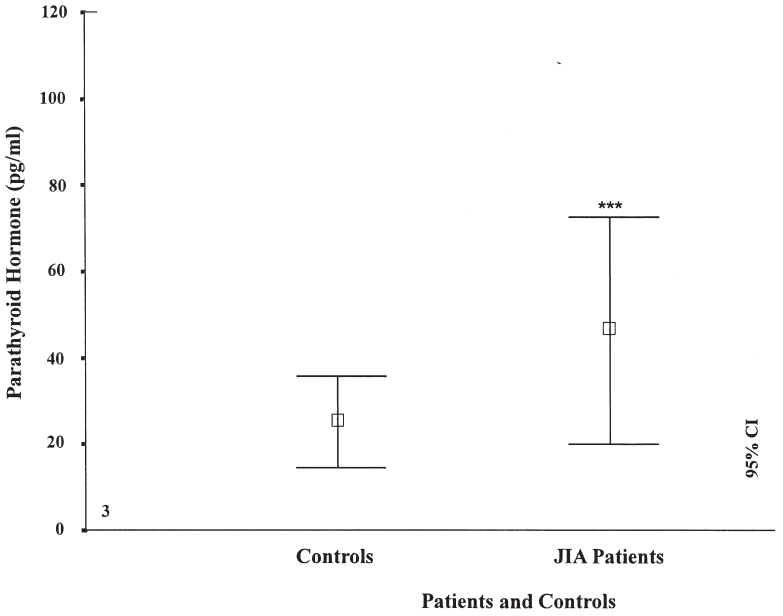

Figure 3. Parathyroid hormone levels (pg/ml) in patients with juvenile idiopathic arthritis (JIA) and controls. **p < 0.005.

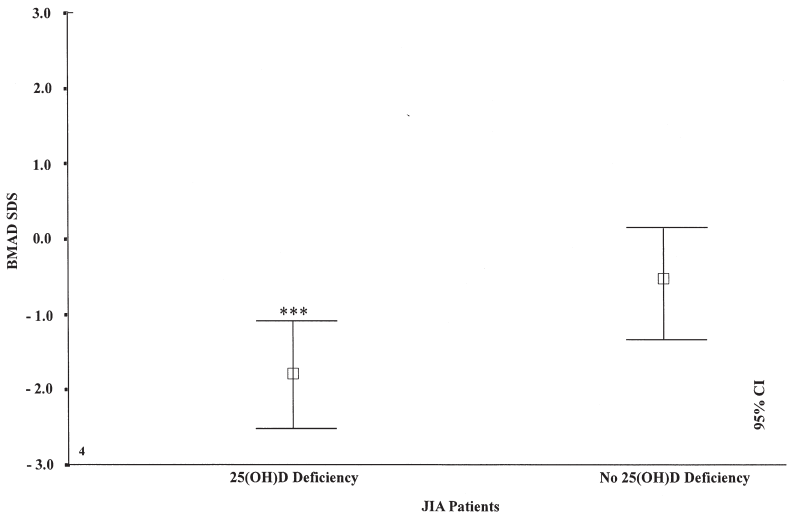

Figure 4. Bone mineral apparent density (BMAD) in patients with juvenile idiopathic arthritis (JIA) with and without 25(OH)D deficiency. ***p < 0.001.

disease activity (r = –0.40, p < 0.005), disease duration (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

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

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[37]. 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[38].

It has also been suggested that vitamin D is involved in immunoregulatory activities[15], 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[39,40].

Hence, higher dosage of 25(OH)D supplementation in patients with more severe JIA subtypes, active disease, or frequent relapses could be considered[41].

In adults it has been reported that vitamin D intake was inversely associated with the risk of rheumatoid arthritis (RA)[42]. 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[43,44]. 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[28].

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[28]. 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[45], 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[13], but contrasts with findings from Pelajo, *et al*[27], 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[46,47], 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[48]; 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[49], we detected, without therapeutic intervention, increased values of PTH. Bianchi, *et al*[50] 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, to 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[30] 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

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

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.

REFERENCES

1. McKenna MJ. Differences in vitamin D status between countries in young adults and the elderly. Am J Med 1992;93:69-77.
2. Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, et al. A global study of vitamin D status and parathyroid function in postmenopausal women with osteoporosis: Baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 2001;86:1212-21.
3. Adami S, Bertoldo F, Braga V, Fracassi E, Gatti D, Gandolini G, et al. 25-hydroxy vitamin D levels in healthy premenopausal women: Association with bone turnover markers and bone mineral density. Bone 2009;45:423-6.
4. Lippi G, Montagnana M, Targher G. Vitamin D deficiency among Italian children. CMAJ 2007;177:1529-30.
5. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
6. Cheng S, Tylavsky F, Kröger H, Kärkkäinen M, Lyytikäinen A, Koistinen A, et al. Association of low 25-hydroxyvitamin D concentrations with elevated parathyroid hormone concentrations and low cortical bone density in early pubertal and prepubertal Finnish girls. Am J Clin Nutr 2003;78:485-92.
7. Lehtonen-Veromaa M, Möttönen T, Irjala K, Kärkkäinen M, Lamberg-Allardt C, Hakola P, et al. Vitamin D intake is low and hypovitaminosis D common in healthy 9- to 15-year-old Finnish girls. Eur J Clin Nutr 1999;53:746-51.
8. Visser M, Deeg DJ, Lips P; Longitudinal Aging Study Amsterdam. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): The Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab 2003;88:5766-72.
9. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or = 60 y. Am J Clin Nutr 2004;80:752-8.
10. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: A review of the current evidence. Arch Pediatr Adolesc Med 2008;162:513-9.
11. Adorini L, Penna G. Control of autoimmune diseases by the vitamin D endocrine system. Nat Clin Pract Rheumatol 2008; 4:404-12.
12. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol 2008;68:261-9.
13. Cutolo M, Otsa K, Uprus M, Paolino S, Seriolo B. Vitamin D in rheumatoid arthritis. Autoimmun Rev 2007;7:59-64.
14. Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiol Rev 1998;78:1193-231.
15. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: New aetiological and therapeutic considerations. Ann Rheum Dis 2007;66:1137-42.
16. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.
17. Baker JF, Baker DG, Toedter G, Shults J, Von Feldt JM, Leonard MB. Associations between vitamin D, disease activity, and clinical response to therapy in rheumatoid arthritis. Clin Exp Rheumatol 2012;30:658-64.
18. 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;31:493-9.
19. Craig SM, Yu F, Curtis JR, Alarcón GS, Conn DL, Jonas B, et al. Vitamin D status and its associations with disease activity and severity in African Americans with recent-onset rheumatoid arthritis. J Rheumatol 2010;37:275-81.
20. 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;56:2143-9.
21. Kerr GS, Sabahi I, Richards JS, Caplan L, Cannon GW, Reimold A, et al. Prevalence of vitamin D insufficiency/deficiency in rheumatoid arthritis and associations with disease severity and activity. J Rheumatol 2011;38:53-9.
22. Haque UJ, Bathon JM, Giles JT. Association of vitamin D with cardiometabolic risk factors in rheumatoid arthritis. Arthritis Care Res 2012;64:1497-504.
23. Rossini M, Maddali Bongi S, La Montagna G, Minisola G, Malavolta N, Bernini L, et al. Vitamin D deficiency in rheumatoid arthritis: Prevalence, determinants and associations with disease activity and disability. Arthritis Res Ther 2010;12:R216.
24. Varenna M, Manara M, Cantatore FP, Del Puente A, Di Munno O, Malavolta N, et al. Determinants and effects of vitamin D supplementation on serum 25-hydroxy-vitamin D levels in patients with rheumatoid arthritis. Clin Exp Rheumatol 2012;30:714-9.
25. Welsh P, Peters MJ, McInnes IB, Lems WF, Lips PT, McKellar G, et al. Vitamin D deficiency is common in patients with RA and linked to disease activity, but circulating levels are unaffected by TNFα blockade: Results from a prospective cohort study. Ann Rheum Dis 2011;70:1165-7.
26. 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;38:2000-4.
27. 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;32:3923-29.
28. Nisar MK, Masood F, Cookson P, Sansome A, Ostör AJ. What do we know about juvenile idiopathic arthritis and vitamin D? A systematic literature review and meta-analysis of current evidence. Clin Rheumatol 2013;32:729-34.
29. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
30. Stagi S, Masi L, Capannini S, Cimaz R, Tonini G, Matucci-Cerinic M, et al. Cross-sectional and longitudinal evaluation of bone mass in children and young adults with juvenile idiopathic arthritis: The role of bone mass determinants in a large cohort of patients. J Rheumatol 2010;37:1935-43.
31. Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyvitamin D in an elderly nursing home population in Boston. Am J Clin Nutr 1990; 51:1075-81.
32. Kröger H, Kotaniemi A, Vainio P, Alhava E. Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. Bone Miner 1992;17:75-85.
33. Kröger H, Vainio P, Nieminen J, Kotaniemi A. Comparison of different models for interpreting bone mineral density measurements using DXA and MRI technology. Bone 1995; 17:157-9.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org

34. Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). J Endocrinol Invest 2006;29:581-93.
35. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170-9.
36. van den Ouweland JM, Vogeser M, Bächer S. Vitamin D and metabolites measurement by tandem mass spectrometry. Rev Endocr Metab Disord 2013; 14: 159-84.
37. Soilu-Hänninen M, Laaksonen M, Laitinen I, Erälinna JP, Lilius EM, Mononen I. A longitudinal study of serum 25-hydroxyvitamin D and intact parathyroid hormone levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. J Neurol Neurosurg Psychiatry 2008;79:152-7.
38. Devaraj S, Yun JM, Duncan-Staley CR, Jialal I. Low vitamin D levels correlate with the proinflammatory state in type 1 diabetic subjects with and without microvascular complications. Am J Clin Pathol 2011;135:429-33.
39. Deluca HF, Cantorna MT. Vitamin D: Its role and uses in immunology. FASEB J 2001;15:2579-85.
40. Fritsche J, Mondal K, Ehrnsperger A, Andreesen R, Kreutz M. Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. Blood 2003;102:3314-6.
41. Maruotti N, Cantatore FP. Vitamin D and the immune system. J Rheumatol 2010;37:491-5.
42. Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG; Iowa Women's Health Study. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. Arthritis Rheum 2004;50:72-7.
43. Andjelkovic Z, Vojinovic J, Pejnovic N, Popovic M, Dujic A, Mitrovic D, et al. Disease modifying and immunomodulatory effects of high dose 1 alpha (OH) D3 in rheumatoid arthritis patients. Clin Exp Rheumatol 1999;17:453-6.
44. Stark LJ, Davis AM, Janicke DM, Mackner LM, Hommel KA, Bean JA, et al. A randomized clinical trial of dietary calcium to improve bone accretion in children with juvenile rheumatoid arthritis. J Pediatr 2006;148:501-7.
45. Nielen MM, van Schaardenburg D, Lems WF, van de Stadt RJ, de Koning MH, Reesink HW, et al. Vitamin D deficiency does not increase the risk of rheumatoid arthritis: comment on the article by Merlino et al. Arthritis Rheum 2006;54:3719-20.
46. El Hayek J, Egeland G, Weiler H. Vitamin D status of Inuit preschoolers reflects season and vitamin D intake. J Nutr 2010;140:1839-45.
47. Huotari A, Herzig KH. Vitamin D and living in northern latitudes — An endemic risk area for vitamin D deficiency. Int J Circumpolar Health 2008;67:164-78.
48. Elsasser U, Wilkins B, Hesp R, Thurnham DI, Reeve J, Ansell BM. Bone rarefaction and crush fractures in juvenile chronic arthritis. Arch Dis Child 1982;57:377-80.
49. Reed A, Haugen M, Pachman LM, Langman CB. Abnormalities in serum osteocalcin values in children with chronic rheumatic diseases. J Pediatr 1990;116:574-80.
50. Bianchi ML, Bardare M, Caraceni MP, Cohen E, Falvella S, Borzani M et al. Bone metabolism in juvenile rheumatoid arthritis. Bone Miner 1990;9:153-62.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2014. All rights reserved.

Downloaded on April 20, 2024 from www.jrheum.org