25-Hydroxyvitamin D Levels and Vitamin D Deficiency in Children with Rheumatologic Disorders and Controls

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ABSTRACT. ***Objective.*** To evaluate the prevalence of vitamin D deficiency, as well as factors associated with serum 25-hydroxyvitamin D [25(OH)D] levels, in children attending a pediatric rheumatology clinic, and to determine whether there was a difference in serum 25(OH)D levels and in vitamin D deficiency between children with autoimmune disorders and nonautoimmune conditions.

Methods. Cross-sectional analysis of serum 25(OH)D levels of patients between the ages of 2 and 19 years, seen between November 2008 and October 2009.

Results. A total of 254 patients were studied (169 autoimmune disorders, 85 nonautoimmune conditions). The mean age of study patients was 12.3 years; 67% were female and 80% were white. In the autoimmune disorders group, 23% had vitamin D deficiency [serum 25(OH)D < 20 ng/ml], and in the nonautoimmune conditions group 14% were vitamin D deficient. The average level of serum 25(OH)D was 28.6 (± 11) ng/ml (range 2 to 59). Age, ethnicity, body mass index, use of supplements, and season were significantly associated with serum levels of 25(OH)D (all $p \leq 0.02$). The OR of patients with autoimmune disorders being vitamin D deficient was 2.3, in relation to patients with nonautoimmune conditions ($p = 0.04$).

Conclusion. Twenty percent of patients attending a pediatric rheumatology clinic were vitamin D deficient. Patients with autoimmune disorders were more likely to be vitamin D deficient than patients with nonautoimmune conditions. Screening of serum 25(OH)D levels should be performed for patients with autoimmune disorders. (First Release July 15 2011; J Rheumatol 2011;38:2000–4; doi:10.3899/jrheum.110123)

Key Indexing Terms:
25-HYDROXYVITAMIN D VITAMIN D DEFICIENCY RHEUMATOLOGY CHILD

Vitamin D has multiple immunosuppressant properties[1]. *In vitro*, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] inhibits the activation of monocytes to dendritic cells, decreasing interleukin 12 (IL-12) production; it inhibits B cell proliferation, decreasing production of antibodies; and it also inhibits T cell proliferation and activation. Many studies have observed that 1,25$(OH)_2$D inhibits the Th1 profile, decreasing IL-2, interferon-γ, IL-1, IL-6, and tumor necrosis factor-α synthesis and promoting Th2 dominance, increasing IL-4, IL-5, and IL-10 synthesis[2,3,4,5,6,7,8,9,10].

Studies in animal models of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) have used 1,25$(OH)_2D_3$ analogs not only to prevent but also to treat ongoing disease[2,4,9,11,12,13,14,15].

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Vitamin D deficiency has been linked to several autoimmune diseases in humans, including IBD, type 1 diabetes, multiple sclerosis, RA, and SLE[2,11,13,16,17,18,19,20,21,22,23,24]. Most studies in humans have documented lower serum levels of 25-hydroxyvitamin D in patients with autoimmune diseases. Serum 25(OH)D levels in adults with SLE are significantly lower than in controls[2,11,16,25,26,27,28].

Considerably less is known about serum levels of 25(OH)D in children with rheumatologic disorders. Our chief aim with this observational study was to determine the prevalence of vitamin D deficiency [defined as serum 25(OH)D < 20 ng/ml][5,29,30,31], as well as factors associated with serum 25(OH)D levels, in children and adolescents attending a pediatric rheumatology clinic. A second aim was to ascertain whether there was a difference in serum levels of 25(OH)D and vitamin D deficiency rates among children with autoimmune disorders as compared to those with nonautoimmune conditions.

MATERIALS AND METHODS

We performed a cross-sectional analysis of serum 25(OH)D levels of patients attending the pediatric rheumatology clinic in the Floating Hospital for Children at Tufts Medical Center between November 2008 and October 2009. All patients who had routine phlebotomy performed were included. Our study was approved by the Institutional Review Board of Tufts Medical Center.

Serum 25(OH)D was measured by liquid chromatography-quadrupole mass spectrometer (Waters Acquity UPLC, Milford, MA, USA, with TQD triple quadrupole mass spectrometer). This method separates and quantifies

circulating 25(OH)D_2 and 25(OH)D_3. The laboratory participates in the College of American Pathologists proficiency testing and the Vitamin D External Quality Assessment Scheme (www.deqas.org; Charing Cross Hospital, London, UK), an international consortium of laboratories set up to ensure the analytical reliability of 25(OH)D. The laboratory also validated the assay using the Standard Reference Material 972 (National Institute of Standards and Technology, Gaithersburg, MD, USA). Interassay coefficients of variation are 6.5%–11% for 25(OH)D_3 over the range of 5–80 ng/ml and 9%–13% for 25(OH)D_2 over the range of 2.5–60 ng/ml. Patients were classified into 2 mutually exclusive categories according to their vitamin D status: deficient [serum 25(OH)D < 20 ng/ml] or nondeficient [serum 25(OH)D level ≥ 20 ng/ml][5,29,30,31].

Information concerning patients' demographics (sex, age, and ethnicity), body mass index (BMI), diagnosis, disease activity, use of medications and supplements, and season of serum 25(OH)D measurement were identified based on the review of medical records.

Patients were classified into 2 distinct groups based on their clinical diagnoses. The first group included patients with definite autoimmune disorders, including juvenile idiopathic arthritis (JIA), juvenile SLE, juvenile dermatomyositis, scleroderma mixed connective tissue disease (MCTD), and vasculitis, while the second included patients who had a nonautoimmune condition (e.g., noninflammatory disorders, infectious diseases, pain amplification syndrome).

Disease activity was evaluated only for patients with autoimmune disorders. This was defined as active or inactive based on the attending physician's assessment at the time of the index clinic visit.

BMI was divided into 2 categories: obese and nonobese. Children were classified as obese if their BMI was ≥ the 95th percentile, and nonobese if BMI was below the 95th percentile[32].

Statistical analyses. Descriptive statistics were used to analyze the data. We determined the prevalence of vitamin D deficiency in the study sample. Univariate analyses were conducted using ANOVA and T-tests to determine the association of categorical and binary variables with serum 25(OH)D levels. A multivariate linear regression was used to analyze variables identified *a priori* associated with serum 25(OH)D levels, including age, supplement use, autoimmune disorder, BMI, ethnicity, and season. A multivariate logistic regression was used to determine the OR of vitamin D deficiency in patients with autoimmune disorders, after adjusting for confounders (supplement use, BMI, ethnicity, and season), identified *a priori*. JMP version 8 (SAS Institute Inc., Cary, NC, USA) was used for data analyses. All tests were 2-sided, and statistical significance was established with an $\alpha < 0.05$.

RESULTS

Sample. A total of 254 patients had serum 25(OH)D measurements performed during the study period; of these, 169 patients (67%) had autoimmune disorders and 85 had nonautoimmune conditions. The average age of all children was 12.3 (± 4.5) years, 67% were female, and 80% were white. There were no differences in various demographic characteristics according to disease group (Table 1).

Vitamin D deficiency. Mean serum level of 25(OH)D in the complete sample was 28.6 (± 11) ng/ml. The range was 2 to 59 ng/ml. Average serum levels of 25(OH)D in patients with autoimmune disorders were 28.1 (± 11.4) ng/ml, compared to 29.7 (± 10.3) ng/ml in patients with nonautoimmune disorders (p = 0.25).

In patients with autoimmune disorders, 23% had vitamin D deficiency, while in patients with nonautoimmune conditions this rate was 14%. The OR of patients with autoimmune disorders being vitamin D deficient, after adjusting for supplement use, BMI, ethnicity, and season, was 2.3, in relation to patients with nonautoimmune disorders (p = 0.04; Table 2).

Variables associated with serum 25(OH)D levels. Age, ethnicity, BMI, season, and use of supplements containing vitamin D were significantly associated with serum 25(OH)D levels, as expected (Table 3).

Serum 25(OH)D and medications. Among patients with autoimmune disorders, 60 (36%) were not taking any medications. Of the remainder, medication use included nonsteroidal antiinflammatory drugs (NSAID; 39, 23%), prednisone (24, 14%), biologic drugs (adalimumab, etanercept, infliximab, anakinra, and rituximab; 24, 14%), disease-modifying antirheumatic drugs (DMARD; methotrexate, cyclosporine, cyclophosphamide, azathioprine, and hydroxychloroquine; 20, 12%), and intravenous immunoglobulin infusions (2, 1%).

Mean serum 25(OH)D levels by each medication used were 29 ng/ml for NSAID, 22 ng/ml for prednisone, 28 ng/ml for biologic drugs, 29 ng/ml for DMARD, 32 ng/ml for intravenous immunoglobulin, and 30 ng/ml for patients taking no medications. Mean serum 25(OH)D levels did not differ in relation to the use of particular medications (p = 0.12).

No patients with nonautoimmune conditions were taking longterm medications (> 1 month), other than vitamins and oral contraceptives.

Serum 25(OH)D and rheumatologic disorders. Mean serum 25(OH)D levels were 29 ng/ml in JIA (n = 124), 21 ng/ml in SLE (n = 18), 29 ng/ml in vasculitis (n = 9), 32 ng/ml in dermatomyositis (n = 8), 21 ng/ml in MCTD (n = 3), 26 ng/ml in scleroderma (n = 3), and 32 ng/ml in Sjögren's syndrome (n = 2). Serum 25(OH)D levels did not vary by diagnosis in patients with autoimmune disorders (p = 0.05).

There were 117 patients (69%) with autoimmune disorders who had active disease. Mean serum 25(OH)D levels did not differ in patients with active (27.9 ± 11.7 ng/ml) or inactive (28.5 ± 10.8 ng/ml) disease (p = 0.78).

In patients with nonautoimmune conditions, mean serum 25(OH)D levels did not differ among diagnoses (p = 0.96).

In the multivariate linear regression, autoimmune disorder was not associated with serum 25(OH)D levels, after adjustment for age, supplement use, BMI, ethnicity, and season (p = 0.06; Table 3).

DISCUSSION

In this sample of children and adolescents with autoimmune and nonautoimmune conditions, we found a high prevalence of vitamin D deficiency. Serum levels of 25(OH)D were associated with age, ethnicity, BMI, season, and use of supplements. After adjustment for confounding variables, patients with autoimmune disorders were 2.3 times more likely to be vitamin D deficient than patients with nonautoimmune conditions; however, there was no difference in mean serum 25(OH)D levels between patients with autoimmune and nonautoimmune disorders.

Table 1. Demographic variables by disease group.

Demographic Data	Autoimmune Disorders, n = 169		Nonautoimmune Disorders, n = 85		p
Age, yrs, mean ± SD	12.3 ± 4.7		12.4 ± 4.3		NS
Female, n %	115	68	56	66	NS
Ethnicity, n %					
White	136	80	68	80	NS
African American	13	8	6	7	
Hispanic	13	8	6	7	
Asian	7	4	5	6	
Body mass index, n %					
Nonobese	145	86	70	82	
Obese	24	14	15	18	NS
Season, n %					
Fall	40	24	14	16	NS
Winter	51	30	27	32	
Spring	40	24	24	28	
Summer	38	22	20	24	
Vitamin D (VD) supplementation, n %					
None	139	82	70	82	
≤ 400 IU VD_3 daily	24	14	13	15	NS
> 400 IU VD_3 daily	6	4	2	2	
Diagnosis, n (%)	JIA 124 (73); SLE 18 (11); Vasculitis (Behçet's disease, Wegener's granulomatosis, Takayasu's arteritis, Henoch-Schönlein purpura) 9 (5); Dermatomyositis 8 (5); Mixed connective tissue disease 3 (2); Scleroderma 3 (2); Sjögren's syndrome 2 (1); Rheumatic fever 1 (0.5); Neonatal lupus 1 (0.5)		Noninflammatory disorders (patello-femoral syndrome, osteochondritis dissecans, meniscus strain, fractures, Osgood-Schlatter, hypermobility and growing pain) 37 (43); Infectious diseases (Lyme, viral infections, bacterial infections) 11 (13); Abnormal laboratory findings 10 (12); Pain amplification syndrome 10 (12); Acrocyanosis 6 (7); Other (asthma, fatigue, arthralgias) 11 (13)		NA

NS: nonsignificant; NA: not applicable.

Table 2. Multivariate logistic regression analysis of vitamin D deficiency [serum 25 (OH)D < 20 ng/ml].

Variable	Estimate	SE	p	OR
Disease (autoimmune disorders)	0.41	0.21	0.04	2.3
Season (fall, winter, and spring)	1.14	0.39	0.003	9.8
Ethnicity (white)	–1.04	0.19	< 0.0001	0.1
Body mass index (nonobese)	–0.50	0.23	0.03	0.4
Supplementation (none)	0.79	0.33	0.02	4.9

Our findings are in part consistent with a large number of cross-sectional studies on vitamin D status and autoimmune rheumatologic diseases in adults, which show lower serum levels of 25(OH)D, or higher rates of vitamin D deficiency, in patients with autoimmune disorders[11,12,14,15,17,19,33,34,35]. Interventional studies also show an interesting effect of vitamin D in autoimmunity. For example, high-dose oral α-calcidiol therapy reduced disease activity in 89% of 19 patients with RA[14]. In another uncontrolled study of 11 adults with systemic sclerosis, $1,25(OH)_2D_3$ administered for a period of 6 months to 3 years was associated with significant improvement in clinical measures[36].

There are few studies in children comparing serum levels of 25(OH)D in patients with autoimmune disorders and nonautoimmune disorders, or healthy controls. One study assessed serum 25(OH)D levels in children with rheumatologic disorders and did not find decreased levels in patients with active or inactive disease. However, in that study serum levels of 25(OH)D ≥ 15 ng/ml were considered normal and no healthy controls were used for comparison[37]. Serum 25(OH)D

Table 3. Multivariate linear regression analysis of variables associated with serum 25(OH)D levels.

Variable	Estimate	SE	p
Age	–0.30	0.13	0.02
Vitamin D supplementation			< 0.0001
None	–5.70	1.18	< 0.0001
≤ 400 IU VD_3 daily	–2.22	1.42	0.12
> 400 IU VD_3 daily	Reference group		
Autoimmune disorder	–1.11	0.60	0.06
Body mass index (nonobese)	2.55	0.80	0.002
Ethnicity (white)	3.92	0.74	< 0.0001
Season			< 0.0001
Fall	–0.26	1.06	0.80
Winter	–3.64	0.92	0.0001
Spring	–2.49	0.99	0.01
Summer	Reference group		

levels have been compared between JIA and healthy controls in 3 different studies; however, results were inconsistent, since 2 of them, from the same group of authors, found a normal range of serum 25(OH)D that did not differ from controls[38,39]; in the other study, children with JIA had serum 25(OH)D levels significantly lower than those in controls[40].

Although there was no statistically significant difference between serum 25(OH)D levels of patients with different autoimmune disorders, the differences found might be clinically meaningful. Patients with MCTD and SLE had lower serum 25(OH)D levels in comparison to other autoimmune disorders. Lower serum levels of 25(OH)D in adult patients with SLE have been reported[2,11,12,15,16,25]. These findings could relate to the photosensitivity associated with these conditions and the special recommendation to use sunscreen and avoid sun exposure. Other possibilities include associated renal disease or medications[15,23,41]. Hence, patients with SLE and MCTD may be at increased risk for vitamin D deficiency. Regular monitoring of serum 25(OH)D levels in this population may therefore be recommended[15,22].

Unlike other studies, we did not find an association between disease activity and serum levels of 25(OH)D in patients with autoimmune disorders. Others have found lower levels of serum 25(OH)D in adult patients with active SLE, in comparison to patients with inactive disease[15,17,19,25], and negative correlations between serum 25(OH)D levels and disease activity in adults with RA[25,33,34]. However, other studies failed to show any correlation between disease activity and serum 25(OH)D levels in adult patients with SLE[12,13,16]. The lack of association between disease activity and serum 25(OH)D levels in our study might be explained by the tool used to measure disease activity, which was based only on the attending physician's assessment, and no structured or composite instrument was used.

Although prednisone use is known to cause reduced serum levels of 25(OH)D[22,40,42], we did not find a significant association between this use and serum 25(OH)D levels. Similar findings were reported by others in adults with SLE[11] or Behçet's disease[43].

Our study had several limitations, including being retrospective, and a lack of information available about diet, sun exposure, and use of sunscreen [all of which influence serum 25(OH)D levels]. One possible explanation for why we did not find a significant difference in serum 25(OH)D levels between patients with autoimmune and nonautoimmune disorders was inadequate statistical power, due to our sample size. Another possibility is that serum 25(OH)D levels actually differ by autoimmune disorder, and this difference was missed when different diagnoses were combined. However, this is the first report comparing serum 25(OH)D levels between children with several autoimmune rheumatologic disorders and controls.

Twenty percent of children and adolescents attending a pediatric rheumatology clinic were vitamin D deficient. Serum 25(OH)D levels were associated with age, ethnicity, BMI, season, and use of supplements. Patients with autoimmune disorders were 2.3 times more likely to be vitamin D deficient than patients with nonautoimmune conditions. Hence, screening of serum 25(OH)D levels should be performed for patients with autoimmune disorders. Future studies are needed evaluating serum 25(OH)D levels and disease activity in childhood rheumatologic disorders.

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