Vitamin D status in children, adolescents, and young adults with Crohn disease

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ABSTRACT

Background: Crohn disease (CD) and vitamin D deficiency are associated with decreased bone mineralization.

Objective: We examined the prevalence of and risk factors for hypovitaminosis D in children, adolescents, and young adults with CD.

Design: Growth, clinical characteristics, vitamin D intake (μg/d), and bone mineral density (g/cm²) were measured in a cross-sectional study of 112 subjects (44 females) who had CD and were 5–22 y of age. Hypovitaminosis D was defined as a serum concentration of 25-hydroxyvitamin D [25(OH)D] < 38 nmol/L.

Results: The mean (±SD) serum concentration of 25(OH)D was 59.7 ± 26.9 nmol/L, and 16% (95% CI: 9.3%, 23%) of the subjects had hypovitaminosis D. Hypovitaminosis D was most prevalent during the winter (31%; P = 0.02), among the African Americans (56%; P = 0.01), in the subjects with CD confined to the upper gastrointestinal tract (44%; P = 0.05), and in the subjects with a greater lifetime exposure to glucocorticoid therapy (23.7 ± 13.5 compared with 17.5 ± 12.2 mg/d; P = 0.05). There was no association between hypovitaminosis D and either bone mineral density (P = 0.10) or average dietary intake of vitamin D (4.6 ± 3.6 μg/d; P = 0.87).

Conclusions: In this sample of pediatric patients with CD, hypovitaminosis D was common and was associated with the winter season, African American ethnicity, CD confined to the upper gastrointestinal tract, and magnitude of lifetime exposure to glucocorticoid therapy. The occurrence of these factors should prompt assessment of 25(OH)D status and clinical care optimized by supplementing subjects who have low serum concentrations. The physiologic relevance of ethnicity on 25(OH)D status in children, adolescents, and young adults with CD remains to be determined. Am J Clin Nutr 2002;76:1077–81.

KEY WORDS Vitamin D, hypovitaminosis D, 25-hydroxyvitamin D, Crohn disease, inflammatory bowel disease, children, adolescents, glucocorticoids, bone mineral density, dual-energy X-ray absorptiometry

INTRODUCTION

Vitamin D is essential for dietary calcium absorption and for maintaining calcium and phosphorous balance to ensure optimal bone mineralization. The 2 major physiologically relevant forms of vitamin D in humans are ergocalciferol (vitamin D₂), which is provided from the diet, and cholecalciferol (vitamin D₃), which is cutaneously synthesized from 7-dehydrocholesterol and is also fortified in milk and other food products (1). Serum 25-hydroxyvitamin D [25(OH)D] represents dietary intake and cutaneous synthesis and is a reliable marker of vitamin D status in humans (2, 3). Associations between hypovitaminosis D and poor bone mineralization are well recognized in the elderly, in postmenopausal women (4), and in adults with Crohn disease (CD) (5, 6). Children and adolescents with CD are at increased risk of impaired bone mineralization (7–10). The peak incidence of CD coincides with adolescence (11, 12), which is a critical period of accretion of bone mass (13) and skeletal maturation. Poor growth and nutritional status (14), delayed pubertal development, increased inflammatory cytokines, and glucocorticoid therapy all commonly occur in pediatric patients with CD and negatively affect bone mineralization (9, 10). Furthermore, malabsorption of dietary vitamin D may occur in CD and other inflammatory disorders that involve the small intestine (15).

Relatively few studies have focused on the vitamin D status of pediatric patients with CD. Therefore, the purpose of this study was to examine the vitamin D status of a large sample of children, adolescents, and young adults with CD. Associations between vitamin D status and clinical characteristics of CD were examined.

SUBJECTS AND METHODS

Subjects

The subjects were patients with CD who received care at The Children’s Hospital of Philadelphia and the Hospital of the University of Pennsylvania. The CD patient database was sorted by street address to generate a randomized computer list that was

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used for invitations to participate in the study. The patients, who were 5–22 y of age and had been diagnosed with CD on the basis of radiologic, histologic, and clinical variables, were enrolled during the 12 mo between September 1995 and August 1996. Subjects were excluded if they had any other chronic illness known to affect growth, pubertal development, or body composition. Informed consent was obtained before the study from the subjects and their parents or guardians, and assent was obtained from subjects < 18 y of age. The Institutional Review Board at The Children’s Hospital of Philadelphia approved the study.

**Anthropometry and Crohn disease activity**

Weight and height were recorded with the use of a digital scale accurate to 0.1 kg (Scaltronix, White Plains, NY) and a stadiometer accurate to 0.1 cm (Hollain Ltd, Croswell, Croyynch, United Kingdom), respectively. Weight and height values were compared with reference standards from the National Center for Health Statistics (Hyattsiville, MD). z Scores (SD scores) were computed for weight-for-age and height-for-age with the use of formulas provided by the National Center for Health Statistics (http://www.cdc.gov/growthcharts). For subjects aged ≥ 20 y, z scores were computed by using an age of 19.9 y.

Anatomical sites of CD involvement were obtained from endoscopic, histologic, and radiologic reports in the medical record, as documented at the time of CD diagnosis, and CD was categorized as 1) upper gastrointestinal CD when involvement was limited to the esophagus, stomach, and small intestine or terminal ileum; 2) lower gastrointestinal CD when involvement was limited to the colon; and 3) mixed CD when both the upper and lower gastrointestinal sites were involved. The clinical severity of CD was assessed at enrollment with the use of the Pediatric Crohn’s Disease Activity Index (PCDAI) (16). The PCDAI score is based on history (30%), physical examination (30%), laboratory data (20%), and height velocity (20%), and scores range from zero to 100. A score of 0–10 corresponds to no disease activity; mild disease activity is represented by a score of 11–30, and moderate-to-severe disease activity is represented by a score > 30. Glucocorticoid exposure was determined from the patients’ medical records and was calculated as the total lifetime steroid exposure (oral and parenteral) for each subject. All dosage forms, except for steroid enemas, were converted to the oral prednisone equivalent. Total exposure in days or months was calculated on the basis of the total number of days or months of glucocorticoid exposure and not on the basis of the total number of days or months of CD duration. Therefore, glucocorticoid exposure was expressed as the cumulative dose in milligrams per day (17).

**Bone mineral density**

Bone mineral density (BMD) of the lumbar vertebrae (anteroposterior view, L1–L4) was measured in each subject with the use of dual-energy X-ray absorptiometry (QDR-2000; Hologic Inc, Wallham, MA). BMD results were expressed as g/cm². Each value was converted to a $z$ score generated from the reference data provided by Hologic Inc. for medium density analysis (18).

**Dietary and serum 25-hydroxyvitamin D**

The dietary intake of vitamin D ($\mu$g/d) was assessed with the use of a 3-d food intake diary (19, 20). A pediatric dietitian instructed the subjects and their families in the technique. Nutrient analysis was performed with the use of Food Processor Plus software, version 6.2 (ESHA Research, Salem, OR). A blood sample for serum 25(OH)D measurement was obtained at enrollment. All serum samples were batched and stored at $-70^\circ$C before being shipped for analysis to the research laboratory of Bruce Hollis at the Medical University of South Carolina (Charleston). Serum 25(OH)D concentrations (in nmol/L) were measured with the use of a radioimmunoassay with a radioiodinated tracer (21). Hypovitaminosis D was defined as a serum 25(OH)D concentration < 38 nmol/L, a cutoff that was based on a range established in Bruce Hollis’s research laboratory.

**Statistical analysis**

The subjects were grouped according to whether they had a normal or low (hypovitaminosis D) serum 25(OH)D concentration. The prevalence and 95% CI of hypovitaminosis D was determined relative to the season during which the blood sample was collected. For the purpose of this study, the seasons of the year were categorized as winter (December–February), spring (March–May), summer (June–August), and fall (September–November). Two-factor analysis of variance was used to compare the 2 groups with respect to BMD $z$ scores (L1–L4), nutritional status (weight-for-age and height-for-age), dietary intake of vitamin D ($\mu$g/d), PCDAI (at enrollment), and lifetime glucocorticoid exposure (mg/d). Chi-square analysis was used to test associations between serum 25(OH)D status and season of the year, CD anatomical site, and African American ethnicity. Logistic regression analysis was used to determine the relative risk of hypovitaminosis D among the African Americans. Statistical significance was defined as $P \leq 0.05$. All analyses were performed with the use of STATA 5.0 software (Stata Corp, College Station, TX).

**RESULTS**

There were 112 subjects (44 females) with a mean (± SD) age of 16.2 ± 4.1 y who enrolled in the present study; they consisted of 101 whites, 9 African Americans (all male), and 2 subjects of other ethnicity. Information about the anatomical site of CD involvement was available for 102 subjects, and most of the subjects (64%) had mixed CD (ie, CD involvement in both upper and lower gastrointestinal sites). Hypovitaminosis D was detected in 18 subjects (16%; 95% CI: 9.3%, 23%). Hypovitaminosis D was significantly more prevalent among the African Americans than among the whites: 56% of the African American subjects had a low serum concentration of 25(OH)D, whereas only 13% of whites had a low concentration ($P = 0.01$). A logistic regression analysis indicated that the relative risk of hypovitaminosis D among African Americans was 4.23 (95% CI: 1.9, 9.17). The other clinical characteristics of the subjects are shown in Table 1.

Of the 112 participants, 35 enrolled in the winter, 25 in the spring, 21 in the summer, and 31 in the fall. Mean serum 25(OH)D concentrations tended to increase as the seasons progressed from winter to fall (Figure 1). The prevalence of hypovitaminosis D was not randomly distributed through the year ($P = 0.02$); the highest prevalence was during the winter season (31%). There was no association between dietary vitamin D and serum 25(OH)D status ($P = 0.87$). There was a higher prevalence of hypovitaminosis D in the subjects with CD involvement limited to the upper gastrointestinal tract (44%; $P = 0.05$) than in the subjects with other patterns of anatomical involvement. The subjects
with hypovitaminosis D had a significantly greater lifetime exposure to glucocorticoid therapy than did those with normal serum 25(OH)D concentrations (23.7 ± 12.2 mg/d; \( P = 0.05 \)). The subjects with hypovitaminosis D tended to have lower BMD \( z \) scores than did those with normal serum 25(OH)D concentrations (−1.8 ± 0.9 compared with −1.4 ± 1.1), however, this association was not significant (\( P = 0.10 \)). No consistent association was detected between hypovitaminosis D and either PCDAI or growth variables (weight-for-age and height-for-age).

### DISCUSSION

In this large sample of children, adolescents, and young adults with CD, 16% had hypovitaminosis D. Hypovitaminosis D was most prevalent during the winter season, among the African Americans, in the subjects with CD confined to the upper gastrointestinal tract, and in the subjects with a greater lifetime exposure to glucocorticoid therapy. The average dietary vitamin D intake did not differ significantly from the adequate intake (5 µg/d) recommended by the National Academy of Sciences (22). Nonetheless, there was wide variation in dietary vitamin D, suggesting that intakes were less than adequate in one-half of the subjects. PCDAI and growth characteristics at enrollment were not associated with serum 25(OH)D status.

Ethnic differences in serum 25(OH)D concentrations have been noted previously: African Americans and Mexican Americans have lower concentrations than do whites (23–26). The reason for this difference and its health sequelae remain to be determined. Among adults, African Americans have lower serum 25(OH)D concentrations, and these concentrations are inversely associated with parathyroid hormone (27). Other calcium-conserving mechanisms may be responsible for the greater BMD and lower hip fracture prevalence observed among African Americans (28). Further studies are required to determine whether African American children and adolescents with CD experience more complications than do their white counterparts, such as inadequate bone mineralization, related to hypovitaminosis D.

A serum 25(OH)D concentration < 39 nmol/L may represent a point in vitamin D status when deficiency begins to unduly stress normal calcium and phosphorous homeostasis. Malabanan et al (29) reported an inverse relation between serum 25(OH)D concentrations and serum parathyroid hormone concentrations in healthy adults. Secondary hyperparathyroidism occurred in >50% of subjects with serum 25(OH)D concentrations of 27.5–39.9 nmol/L but resolved after vitamin D and calcium supplementation (29). Harris and Dawson-Hughes (24) similarly observed an inverse relation between plasma 25(OH)D concentrations and serum parathyroid hormone concentrations, with distinct hyperparathyroidism when serum 25(OH)D concentrations fell below 30 nmol/L in healthy, young adult African American and white women. Docio et al (30) reported that serum parathyroid hormone concentrations decreased after vitamin D supplementation in healthy children with a serum 25(OH)D concentration < 25–30 nmol/L. Driscoll et al (6) found hypovitaminosis D in two-thirds of a sample of adult patients with CD (\( n = 82 \)). Among the subjects with low serum 25(OH)D concentrations, there was a subgroup with osteomalacia that histologically improved in association with oral supplementation with vitamin D and normalization of serum 25(OH)D status (6). However, measurable effects of hypovitaminosis D on BMD have not been universally observed (31).

### TABLE 1

Clinical characteristics of subjects with normal serum 25-hydroxyvitamin D [25(OH)D] concentrations and of subjects with hypovitaminosis D

<table>
<thead>
<tr>
<th></th>
<th>Normal 25(OH)D concentration</th>
<th>Hypovitaminosis D</th>
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<tbody>
<tr>
<td></td>
<td>Males (n = 57; 4 AA)</td>
<td>Females (n = 37; 0 AA)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>15.62 ± 3.23</td>
<td>15.98 ± 3.91</td>
</tr>
<tr>
<td>HAZ</td>
<td>−0.89 ± 1.14</td>
<td>−0.18 ± 1.26</td>
</tr>
<tr>
<td>WAZ</td>
<td>−0.88 ± 1.12</td>
<td>−0.11 ± 1.12</td>
</tr>
<tr>
<td>BMD 2 score</td>
<td>−1.72 ± 1.13</td>
<td>−0.96 ± 0.97</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/L)</td>
<td>69.48 ± 29.12</td>
<td>60.52 ± 14.85</td>
</tr>
<tr>
<td>Dietary vitamin D (µg/d)</td>
<td>4.68 ± 3.23</td>
<td>4.49 ± 4.72</td>
</tr>
<tr>
<td>PCDAI</td>
<td>11.39 ± 10.25</td>
<td>11.98 ± 15.55</td>
</tr>
<tr>
<td>Lifetime glucocorticoids (mg/d)</td>
<td>18.28 ± 11.84</td>
<td>16.31 ± 12.82</td>
</tr>
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\( ^{1}z \pm SD; \) HAZ, height-for-age \( z \) score; WAZ, weight-for-age \( z \) score; BMD, bone mineral density of the lumbar vertebrae (L1–L4); PCDAI, Pediatric Crohn’s Disease Activity Index obtained at enrollment; AA, African Americans. There was no significant main effect of vitamin D status or sex and no significant status-by-sex interaction for any variable on the basis of two-factor ANOVA except for a significant main effect of sex on BMD \( z \) score (\( P = 0.03 \)).

\( ^{2} \)Cumulative lifetime exposure to steroids.

### FIGURE 1

Mean (± SD) 25-hydroxyvitamin D concentrations (nmol/L) by season (■) and the prevalence (%) of hypovitaminosis D (■) in subjects with Crohn disease. The percentage of subjects with hypovitaminosis D varied by season (\( P = 0.02; n = 112 \)).
Seasonal and geographic variations in serum vitamin D status have been reported previously (30, 32, 33); however, the effects on long-term bone mineralization remain unclear. The third National Health and Nutrition Examination Survey found that 13% of healthy adults who lived in the northern latitudes of the United States during the months corresponding to the fall season had serum 25(OH)D concentrations ≤ 38 nmol/L (34). Chinese infants born in northern latitudes during seasons with limited sunlight had lower serum 25(OH)D concentrations and less wrist ossification at birth than did infants born in southern latitudes with greater sunlight (35). However, none of the infants developed clinical or radiologic rickets, and oral supplementation with vitamin D improved serum 25(OH)D status (35). Vogelsang et al (5) prospectively measured serum 25(OH)D concentrations during winter and summer in a group of adult European patients with CD and found decreased bone mineral content in the summer months that correlated with low 25(OH)D concentrations during the previous winter. These findings linked serum 25(OH)D concentrations with decreased bone mineralization in a subsequent season. Decreased BMD is prevalent in patients with CD and originates from many factors, including chronic glucocorticoid therapy, malnutrition, nutrient malabsorption, chronic inflammatory cytokines, and delayed skeletal maturation (7, 10, 36, 37). Therefore, to optimize a nutritional environment that supports bone mineralization in children and adolescents with CD, vitamin D status should be assessed and supplementation should be considered in those with low concentrations.

In this sample of pediatric patients with CD, dietary vitamin D was not associated with serum 25(OH)D concentrations. The average oral intake of vitamin D was ≈ 5 μg/d, which is considered to be an adequate intake for healthy subjects (22). Nonetheless, the wide variation also suggested that dietary vitamin D may have been inadequate in one-half of the subjects. Few foods naturally contain vitamin D (1), and there is a wide variation in the actual vitamin D content of foods fortified with vitamin D (38, 39). Therefore, maintenance of normal serum 25(OH)D concentrations in pediatric patients with CD may necessitate higher dietary intakes of vitamin D than the 5 μg/d considered adequate in healthy children and adolescents (22). Hypovitaminosis D was more prevalent in the subjects with CD confined to the upper gastrointestinal tract. However, the anatomical classification used in the present study was based on information obtained before the study; the natural progression of CD or remission secondary to medical therapy may have modified the site of active disease at the time of the study. Absorption of dietary vitamin D occurs in the small intestine (40) and may be impaired after intestinal resection (41) and in chronic inflammatory disorders involving the small intestine (15). Therefore, patients with anatomical involvement of CD in the upper gastrointestinal tract should be considered at risk of malabsorption of vitamin D and of a low 25(OH)D concentration.

Hypovitaminosis D was associated with a greater lifetime exposure to glucocorticoid therapy. Lifetime steroid exposure (mg/d) reflected cumulative therapy with glucocorticoids since CD diagnosis. Because glucocorticoids are frequently used to induce remission in active CD (42, 43), lifetime steroid exposure was also considered an index of lifetime CD severity. Undocumented glucocorticoid therapy may have resulted from prescriptions obtained by telephone or by nonstandardized maintenance and weaning of steroids by different care providers. However, because it was regular practice to document all practitioner-patient interactions, non-documentation of glucocorticoid therapy should have been minimal. Active CD is frequently associated with anorexia and decreased nutrient intake (44, 45). Fear of gastrointestinal discomfort from lactose intolerance (46, 47) may lead to avoidance of the dairy foods that are commonly supplemented with vitamin D (38, 39). Furthermore, increased CD activity may be associated with physical inactivity, which leads to reduced exposure to sunlight, thereby further compromising vitamin D intake.

25(OH)D has a short serum half-life compared with the time required for measurable accretion of BMD. Our findings suggest that children and adolescents with CD should be considered at risk of hypovitaminosis D. Concomitant assessment of the serum parathyroid hormone concentration, which is considered a specific indicator of vitamin D deficiency (29), may have improved our interpretation of the metabolic significance of hypovitaminosis D in this sample of pediatric patients with CD. The prevalence of secondary hyperparathyroidism that is responsive to vitamin D and calcium supplementation markedly increases at serum 25(OH)D concentrations < 39.9 nmol/L (29), which is within the range of the cutoff used in the present study.

In conclusion, hypovitaminosis D was prevalent in this large sample of children, adolescents, and young adults with CD. The factors associated with hypovitaminosis D were winter season, African American ethnicity, anatomical involvement of CD confined to the upper gastrointestinal tract, and magnitude of lifetime exposure to glucocorticoid therapy. Nutritional status and dietary vitamin D intake within the range recommended for healthy subjects did not correlate with serum 25(OH)D status. Therefore, to optimize nutritional care, serum 25(OH)D concentrations should be assessed in children, adolescents, and young adults with CD, and vitamin D supplementation should be considered in those patients with low concentrations. The physiologic relevance of ethnicity to the 25(OH)D status of patients with CD remains to be determined.

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REFERENCES