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Vitamin D Status in Children and Young Adults With Inflammatory Bowel Disease

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Abstract

OBJECTIVES—Previous studies of vitamin D status in pediatric patients with inflammatory bowel disease have revealed conflicting results. We sought to report (1) the prevalence of vitamin D deficiency (serum 25-hydroxy-vitamin D concentration ≤15 ng/mL) in a large population with inflammatory bowel disease, (2) factors predisposing to this problem, and (3) its relationship to bone health and serum parathyroid hormone concentration.

PATIENTS AND METHODS—A total of 130 patients (8–22 years of age) with inflammatory bowel disease, 94 with Crohn disease and 36 with ulcerative colitis, had serum 25-hydroxy-vitamin D, intact parathyroid hormone, and lumbar spine bone mineral density (using dual-energy x-ray absorptiometry) measured at Children's Hospital Boston.

RESULTS—The prevalence of vitamin D deficiency was 34.6%. Mean serum 25-hydroxy-vitamin D concentration was similar in patients with Crohn disease and ulcerative colitis, 52.6% lower among patients with dark skin complexion, 33.4% lower during the winter months (December 22 to March 21), and 31.5% higher among patients who were taking vitamin D supplements. Serum 25-hydroxy-vitamin D concentration was positively correlated with weight and BMI *z* score, disease duration, and serum albumin concentration and negatively correlated with erythrocyte sedimentation rate. Patients with Crohn disease and upper gastrointestinal tract involvement were more likely to be vitamin D deficient than those without it. Serum 25-hydroxy-vitamin concentration was not associated with lumbar spine bone mineral density *z* score or serum parathyroid hormone concentration.

CONCLUSIONS—Vitamin D deficiency is highly prevalent among pediatric patients with inflammatory bowel disease. Factors predisposing to the problem include having a dark-skin complexion, winter season, lack of vitamin D supplementation, early stage of disease, more severe disease, and upper gastrointestinal tract involvement in patients with Crohn disease. The long-term significance of hypovitaminosis D for this population is unknown at present and merits additional study.

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Keywords

vitamin D deficiency; 25-hydroxy-vitamin D; inflammatory bowel disease; pediatric; bone mineral density; parathyroid hormone

Vitamin D is essential for bone mineralization throughout life. Severe deficits cause rickets in children[1] and osteomalacia in adults.[2] 25-Hydroxy-vitamin D (25OHD) is the most abundant metabolite of this vitamin in the human body and indicative of overall vitamin D status.[3] In both healthy adults[4,5] and children,[6,7] low 25OHD values result in secondary hyper-parathyroidism and increased bone resorption. Low 25OHD concentrations have been associated with decreased bone mineral density (BMD) in previous studies of healthy adults[8,9] and adolescents.[10] Children and adolescents with inflammatory bowel disease (IBD) have a higher prevalence of low BMD when compared with healthy peers.[11–16] Poor nutritional status,[15,16] delayed growth,[14,15] corticosteroid administration,[11,12,16] and the inflammatory process itself[12,17] have been reported as risk factors for this condition in children with IBD. The contribution of hypovitaminosis D to low BMD in children with IBD has not been systematically studied to date to our knowledge.

Data regarding the vitamin D status of children with IBD are limited.[18–20] Issenman et al[20] found normal 25OHD concentrations in children with Crohn disease (CD). Gokhale et al[19] reported lower 25OHD concentrations in children with CD than in those with ulcerative colitis (UC), but they were still within the reference range. Sentongo et al[18] found a 25OHD concentration ≤15 ng/mL in 16% of children with CD, lower concentration in patients with upper gastrointestinal tract (UGI) disease and greater lifetime corticosteroid exposure, and no relationship between 25OHD concentration and vitamin D intake.

Available reports on the vitamin D status of adults with CD place the prevalence of 25OHD concentration ≤15 ng/mL between 22% and 70%, depending on the study.[21–31] Serum 25OHD concentration was found to be <10 ng/mL in 8% to 45% of adults with CD.[21,22,24,26] One study reports a negative relationship among disease duration, Crohn Disease Activity Index, ferritin, C-reactive protein, cholesterol,[24] and 25OHD concentration. Other studies report that smoking[21] and small bowel resection[30,32] are also negatively correlated with 25OHD concentration, whereas sunlight exposure and nutritional status are positively correlated.[29] Fewer studies have described the vitamin D status of adults with UC compared with those with CD. Serum 25OHD concentrations have been found to be normal in some studies of patients with UC,[33,34] whereas others report serum 25OHD concentrations <12 ng/mL in 15%.[25] In one study,[22] the serum 25OHD concentration was <10 ng/mL in 45% of adult patients with UC and was not different from that in patients with CD.

We examined the prevalence of vitamin D deficiency (serum 25OHD ≤15 ng/mL) in a sample of pediatric patients with IBD cared for in a tertiary care medical center. In addition, we examined the influence of specific patient and disease characteristics on their vitamin D status. Lastly, we examined the relationship between the patients' vitamin D status and their lumbar spine BMD (LSBMD) and serum parathyroid hormone (PTH) concentration.

METHODS

Patient Sample and Data Collection

In this cross-sectional study of vitamin D status, 130 patients with IBD, ages 8 to 22 years, cared for at Children's Hospital Boston, had 25OHD, PTH, and serum calcium

concentrations, as well as LSBMD measured ≤6 months before or after their 25OHD assessments.

25OHD, PTH, and serum calcium were measured prospectively throughout the year between February of 2003 and January of 2005. The calendar year was divided into 4 seasons: winter (December 22 to March 21), spring (March 22 to June 21), summer (June 22 to September 21), and fall (September 22 to December 21). The season during which the 25OHD concentration measurement took place was recorded for each patient. Hematocrit, erythrocyte sedimentation rate (ESR), and serum albumin concentrations were obtained either at the same time as, or within a few days of, vitamin D measurement.

All of the patients had their LSBMD measured using dual-energy x-ray absorptiometry (DXA) (Hologic, QDR 4500, Hologic Inc, Bedford, MA) in our General Clinical Research Center (GCRC), as part of the screening phase of a clinical trial of a therapeutic agent to improve BMD in children, adolescents, and young adults with IBD. Inclusion criteria for this trial included the finding of LSBMD *z* score (zLSBMD) −1.0 SD or less. Patients screened for participation in the trial were unselected and self-referred. The protocol for this trial was approved by the Children's Hospital Committee on Clinical Investigation, and patients gave informed consent and assent (wherever appropriate) for any research interventions. Sixty of the above patients qualified and enrolled in the trial, and the above-mentioned laboratory values were obtained during enrollment. The remaining 70 did not enroll (either did not qualify [42] or declined enrollment [28]), and the same laboratory values were obtained during a regular clinic visit, as part of a quality improvement nursing initiative in our IBD center. All of the patients had their vitamin D status evaluated, regardless of their BMD status. The same assays and methods were used for all of the measurements. As expected, the 70 nonenrolled patients had higher mean zLSBMD than the enrolled (−0.6 ± 1.1 vs −1.9 ± 0.8; $P < .001$). To examine the potential for patient selection, we compared the mean serum 25OHD concentration in these 2 groups of patients and found it to be similar (21.3 ± 10.8 in the enrolled patients vs 20.7 ± 10.8 in the nonenrolled patients; $P = .69$).

Data Extraction

Two researchers (H.M.P. and B.H.) obtained data from patients' medical charts. Data collected retrospectively included disease diagnosis, demographic information, height, weight, and zLSBMD (obtained from DXA reports), disease duration (in months), lifetime corticosteroid exposure (in milligrams), information regarding vitamin D supplementation, any surgical intervention up to the date of the 25OHD measurement, and disease location, extent, and behavior. Laboratory values including serum albumin, hematocrit, ESR, and calcium were also recorded. The selection of the data to be obtained was based on literature reports of risk factors for hypo-vitaminosis D and our clinical experiences and hypotheses.

Population and Clinical Characteristics

Patients' weight was measured on a Scale-Tronix digital scale (Scale-Tronix, Inc, White Plains, NY), calibrated at least weekly, either in the outpatient gastroenterology clinic or in the GCRC of the hospital. Patients' height was measured on a Holtain stadiometer (Holtain Ltd, Crymych, Wales), calibrated daily either in the outpatient gastroenterology clinic or the GCRC. Weight and height measurements were performed either on the same day as, or within a few days of, the 25OHD measurements. BMI was calculated using the Epi Info Database and Statistics software for public health professionals (Centers for Disease Control and Prevention, Atlanta, GA, dated September 7, 2004). Weight *z* score (zWt), height *z* score (zHt), and BMI *z* score (zMBI) were calculated using the same program. *z* score represents the distance, positive or negative, in SDs, of the subject's anthropometric

measurements (height, weight, and BMI) from normal values, corrected for age and gender. For patients >20 years of age, *z* scores were calculated using an age of 20 years. Patients were considered to be taking vitamin D supplements if they were taking any preparation containing vitamin D (including multivitamins) at any time during the 3 months before the 25OHD measurement. Information regarding vitamin D supplementation was obtained from medical charts. Clinicians and support staff in our department routinely record all of the medications and supplements that the patients take, including dosing information and brand names of supplements when possible, in the patient's chart during outpatient visits. Based on this information, we were able to determine that all of the patients who reported taking vitamin D supplements were taking between 400 and 800 international units (IUs) of vitamin D per day through supplements. Because of the retrospective nature of this study, we were unable to obtain information regarding dietary vitamin D intake.

The diagnosis of CD, UC, and indeterminate colitis was established by standard clinical, endoscopic, and radiographic criteria.[35,36] Three patients who had the diagnosis of indeterminate colitis at the time of 25OHD measurement were given the diagnosis of UC for the purpose of data analysis. These patients had skip lesions in the colon but absence of lesions in the ileum and UGI tract, no histologic evidence of granulomas, and behavior of their disease typical of UC. Only histologic evidence of granulomas was considered when classifying CD as involving the UGI tract.

Disease duration was measured in months from endoscopic diagnosis to 25OHD measurement. Lifetime corticosteroid exposure was calculated as the total amount in milligrams of parenteral or enteral corticosteroids received from diagnosis to the date of 25OHD measurement. All of the corticosteroids were converted to prednisone equivalents. Two researchers (a gastroenterologist, H.M.P., and a trained research assistant, B.H.) calculated corticosteroid exposure. One researcher (H.M.P.) documented surgical resection of any part of the small or large intestine in both CD and UC patients at any time until 25OHD measurement. Ten patients had resections of ileum, and the resected ileum measured from 1 to 20.3 cm. Because of both the small size of the ileum excised and the small total number of patients with ileal resections, we treated ileal resection as dichotomous (yes or no). CD was classified according to its behavior and the development of complications, following the Vienna criteria,[37] by the same researcher (H.M.P.). This set of criteria has been widely used by gastroenterologists to describe 3 distinct CD phenotypes: (1) noncomplicated, inflammatory; (2) fistulizing (penetrating disease with fistulas and abscesses development); and (3) fibrostenotic disease (with strictures and narrowing across parts of the gastrointestinal tract).

Laboratory Tests

Serum 25OHD was measured in nanograms per milliliter using the Nichols Advantage chemiluminescence-based competitive protein-binding assay (Nichols Institute Diagnostics, San Clemente, CA). The sensitivity of the assay is estimated to be ≤4 ng/mL. The lowest reportable value for this assay is 7 ng/mL and the highest is 120 ng/mL. The reference range, which Nichols Diagnostics gives for 25OHD values in New England, is 10 to 64 ng/mL. The within-run variation is estimated to be between 3% and 4.5% (mean: 3.75%) and the total imprecision between 6.4% and 14.5% (mean: 9.65%; Nichols Advantage product insert 2003). In this study, we considered serum 25OHD concentration ≤15 ng/mL as representing vitamin D deficiency, following the majority established definition, and in keeping with reports on vitamin D status in children with IBD.[18] We considered serum 25OHD concentration ≤8 ng/mL as representing severe vitamin D deficiency following the definition of severe deficiency in other studies of children in New England, including a study of adolescents from our hospital.[38]

Serum PTH concentration was measured using the Nichols Advantage Intact PTH Assay (Nichols Institute Diagnostics), a 2-site chemiluminescence immunoassay. Results are reported in picograms per milliliter. The calculated sensitivity of the assay is 1 pg/mL. The reference range is between 10 and 65 pg/mL. The intra-assay variation is calculated to be between 3.8% and 12.5% (mean: 6.2%) and the interassay variation between 7.5% and 9.2% (mean: 7.9%; Nichols Advantage product insert 2003).

Hematocrit was measured in an automated analyzer, either Advia-120 or Advia-2120 (Bayer Diagnostics, Tarrytown, PA), and ESR was measured using ESR analyzer Vesmatic 20 (Clinical Data, Inc, Smithfield, RI), according to standard protocol. Hematocrit was reported in percentages and ESR in millimeters per hour. Serum albumin and calcium concentrations were measured in a Roche/Hitachi 917 chemistry analyzer (Roche Diagnostic Corporation, Indianapolis, IN) according to standard protocol. Serum albumin was reported in grams per deciliter and serum calcium in milligrams per deciliter.

BMD Measurement

LSBMD was measured using a Hologic QDR 4500 dual energy radiograph absorptiometry scanner (Hologic Inc, Bedford MA), with Delphi software upgrade. Pediatric software was used in those subjects ≤18 years of age. For the calculation of zLSBMD, the manufacturer used a large cross-sectional sample of Canadian children and adolescents for patients ≤18 years of age,[39] and densitometry data obtained from the third National Health and Nutrition Examination Survey for older patients. The scanner is calibrated daily, using a quality control anthropomorphic spine phantom, provided by the company. BMD is reported in grams per centimeter squared. The anteroposterior view of L1 to L4 vertebrae was used in calculating the LSBMD and BMD *z* score.

Statistical Analysis

Descriptive statistics for clinical characteristics and laboratory values were tabulated for the entire study sample and separately for patients with CD and UC. The serum 25OHD concentration showed a skewed distribution and was, therefore, log transformed for analyses.

To evaluate simple bivariate associations among serum 25OHD concentration, vitamin D deficiency, and predictor variables, we used 2-sample *t* tests, 1-way analysis of variance, simple linear regression, Pearson or Spearman's correlation coefficients, χ^2 tests, and simple logistic regression as appropriate to the nature and distribution of the variables. We constructed a multiple linear regression model for log-transformed serum 25OHD concentration using all of the predictors of interest, whether significant or not in the simple regression. The predictors of interest included diagnosis, ethnicity, season, receiving vitamin D supplement or not, zBMI, serum albumin concentration, ESR, lifetime corticosteroid exposure, bowel resection, and disease duration. Confounding relationships were evaluated by whether the coefficients and statistical significance changed substantially when a suspected confounder was added or removed from the model. The effects in log units (change in log serum 25OHD concentration) were converted to percentage units by 100% × [exp (change in log serum 25OHD concentration) − 1]. A multiple logistic regression model was also constructed for vitamin D deficiency using the same set of predictors. The corresponding associations were expressed as odds ratios (ORs). Statistical analyses were performed by SPSS 12.0 (SPSS Inc, Chicago, IL) and SAS 9.0 (SAS Institute, Cary, NC). A 2-sided *P* value of <.05 indicated statistical significance.

RESULTS

Participant Characteristics

The sample was composed of 130 participants with IBD, 94 (72.3%) with CD, and 36 (27.7%) with UC (Table 1). Age, gender, and race distribution were similar in patients with CD and UC. Compared with patients with UC, patients with CD had significantly lower mean zHt, zWt, and zBMI ($P \leq .03$; Table 1). zLSBMD of patients with CD was of a wider range, and the mean was lower than that of patients with UC, but this did not reach significance levels ($P = .10$). Disease duration in months from diagnosis to 25OHD measurement was similar in the 2 groups of patients. Mean lifetime corticosteroid exposure in milligrams from diagnosis to serum 25OHD measurement tended to be lower in patients with CD than those with UC, although it did not reach significance ($P = .09$). The proportion of patients who had intestinal resections from diagnosis to the time of vitamin D measurement was similar, as well. Among patients with CD, 37.3% had documented UGI involvement with histologic evidence of granulomas, and 30.8% had complicated disease (13.8% had fistulizing disease, 11.7% had fibrostenotic disease, and 5.3% had both). Patients with CD also had significantly lower mean serum albumin concentration ($P = .02$) and significantly higher mean ESR ($P = .001$). Their hematocrit values were similar to those of patients with UC.

Vitamin D Status and Related Laboratory Measures

The prevalence of vitamin D deficiency and severe deficiency was 34.6% and 10.8%, respectively, in our sample of patients with IBD (Table 2). Compared with patients with UC, patients with CD did not have a statistically significantly higher prevalence of vitamin D deficiency or severe deficiency. The mean serum concentrations of 25OHD, PTH, and calcium were similar between patients with CD and UC. The number of patients with CD and UC taking vitamin D supplements was similar. The distribution of serum 25OHD assessment across the 4 seasons did not differ between patients with CD and UC, and it was roughly uniform across the 4 seasons ($P = .65$, χ^2 test).

Variables Associated With Serum 25OHD Concentration

We first examined whether significant simple associations existed between serum 25OHD concentration (log transformed) and participant characteristics and laboratory values. We found several such associations (Table 3).

Specifically, serum 25OHD concentration was 52.6% lower among persons with darker skin complexion ($P = .02$), 33.4% lower during the winter months (December to March; $P < .001$), and 31.5% higher among those who were receiving vitamin D-containing supplements compared with those who were not ($P = .02$). The serum 25OHD concentration was also 9.1% higher for each unit increase in zWt ($P = .02$), 8.6% higher for every unit increase in zBMI ($P = .04$), 46.8% higher for every gram per deciliter increase in serum albumin concentration ($P < .001$), and 0.7% lower for every millimeter per hour increase in ESR ($P = .01$). A borderline positive association was found with disease duration ($P = .08$). Note that serum 25OHD concentration was not significantly higher in patients with UC as compared with those with CD ($P = .10$).

We fitted a multiple linear regression model with log-transformed serum 25OHD concentration as the dependent variable and including as covariates all of the variables examined for simple association except for age at the time of the serum 25OHD measurement, gender, and hematocrit (which were not hypothesized predictors of interest and nonsignificant in the simple association) and zHt and zWt (which were components of zBMI and, thus, highly correlated with zBMI; Table 3). Ethnicity ($P = .02$), season ($P < .$

001), and serum albumin concentration (P = .01) remained significant, with adjusted effect size similar to that in simple unadjusted regressions. In contrast, zBMI (P = .67), ESR (P = .97), and vitamin D supplementation (P = .67) became non-significant, with their effect size attenuated after adjusting for other predictors. Bowel resection (P = .98) and disease duration (P = .13) remained nonsignificant. Note that diagnosis (CD versus UC) was not significant in either simple or multiple regression.

Variables Associated With Vitamin D Deficiency

Simple bivariate associations between predictors and vitamin D deficiency (serum 25OHD concentration ≤15 ng/mL) were examined. Consistent with the results for continuous serum 25OHD concentration, vitamin D deficiency was more likely to occur in winter months (OR: 4.1; 95% confidence interval [CI]: 1.9 to 9.2; P < .001), in patients who were newly diagnosed (<12 months; OR: 2.3; 95% CI: 1.1 to 4.8; P = .03), and in patients with lower serum albumin concentration (P = .005; with albumin <3.5 showing the highest OR for vitamin D deficiency; OR: 5.0; 95% CI: 1.9 to 13.3). In a multiple logistic regression model with the same set of predictors as used in the multiple linear regression model for continuous serum 25OHD concentration, only winter season (OR: 5.1; 95% CI: 1.9 to 13.8; P = .002) and albumin concentration (when albumin was <3.5; OR: 5.1; 95% CI: 1.3 to 19.7; P = .04) remained as significant predictors of vitamin D deficiency. Although newly diagnosed disease became statistically nonsignificant by multiple regression (OR: 1.9; 95% CI: 0.7 to 5.2; P = .18), the attenuation in the OR was small, and the 95% CI was skewed toward the existence of an effect. Diagnosis (CD versus UC) was not significantly associated with vitamin D deficiency in either simple or multiple regression.

Relationships Between Predictors

In an effort to explain the confounding relationships in the multiple regression models, we examined the associations between predictors. ESR, zBMI, disease duration, and vitamin D supplementation had significant simple associations with serum 25OHD concentration, but their coefficients were attenuated and became non-significant after adjusting for other predictors in the multiple regression. This attenuation is likely because of the independent strong association of all of these variables with albumin concentration, which, as noted above, is a strong predictor of serum 25OHD concentration. For the ESR and albumin correlation, Spearman's ρ (r) = −0.52 (P < .001) for the zBMI and albumin correlation r = 0.28 (P = .002). We speculate that albumin concentration is a stronger predictor of serum 25OHD concentration than zBMI and ESR, because it reflects both nutritional status and severity of inflammation. Patients with longer-standing diagnosis had higher albumin concentrations than newly diagnosed patients (4.04 ± 0.52 vs 3.66 ± 0.58; Mann-Whitney P < .001). This association could be explained by the fact that, in time, therapeutic interventions place inflammation under control and improve nutritional status and, thus, albumin concentration. Vitamin D supplement users had a significantly higher serum albumin concentration than nonusers (4.0 ± 0.5 vs 3.6 ± 0.7; P = .02). This could be explained by the assumption that vitamin D supplementation is a surrogate marker for further therapeutic interventions and other medications, which, in turn, reduce inflammation and improve nutritional status, thus increasing albumin concentration. In summary, in this sample of patients with IBD, among the predictors examined, ethnicity, season, and albumin concentration are strong independent predictors of vitamin D status.

Subgroup Analyses by Diagnosis

We performed similar analyses in patients with CD. For the continuous (log-transformed) serum 25OHD concentration, a significant simple association was found with season (winter versus other, P = .001), albumin concentration (P < .001), ESR (P = .04), and vitamin D supplementation (P = .004). In the multiple linear regression, season (P < .001) and albumin

concentration (P = .001) remained significant predictors of serum 25OHD concentration. For vitamin D deficiency, a significant simple association was found with season (P = .002), albumin concentration category (P = .004), and UGI involvement (P = .04). Patients with UGI involvement were 2.6 (range: 1.0–6.6) times as likely to be vitamin D deficient as patients without UGI involvement. All 3 of the variables remained significant in the multiple logistic regression ($P \leq .03$).

We also examined simple relationships of the above predictors and serum 25OHD concentration in patients with UC. Here, ethnicity (P = .001) was a significant predictor; disease duration (P = .05 and a positive association) and season (P = .09) were borderline significant; whereas albumin concentration (P = .49), zBMI (P = .48), and vitamin D supplementation (P = .64) were not significant. Serum albumin concentration was not associated with serum 25OHD concentration in patients with UC, because albumin concentrations were consistently normal in these patients, leading to limited variability in albumin concentration and greater difficulty detecting this association. We did not perform multiple regression analysis for serum 25OHD concentration or any analyses for vitamin D deficiency because of the limited sample size of patients with UC.

Relationship Between Serum 25OHD Concentration and Spinal BMD *z* Score

We did not find a significant relationship between serum 25OHD concentration and zLSBMD (Spearman's $\rho = 0.05$; P = .58). Similarly, patients who were vitamin D deficient were not at a significantly higher risk of low BMD (zLSBMD ≤ -1) than patients who were vitamin D sufficient (OR: 1.1; 95% CI: 0.5 to 2.5; P = .73). The observed seasonal variation in serum 25OHD concentrations was not matched with a seasonal variation of BMD measurements. Mean zLSBMD did not differ between winter/spring and summer/fall (winter/spring zLSBMD: -1.2 ± 1.2; fall/summer zLSBMD: -1.4 ± 1.1; Mann-Whitney P = .79).

To account for effects of puberty, we evaluated the relationship between serum 25OHD concentration and zLSBMD separately in patients ≤18 years (n = 112) and those >18 years (n = 18), and we still did not find it to be significant (Spearman's ρ (r) = 0.02, P = .84 in patients ≤18 years; r = 0.18, P = .48 in patients >18 years).

Relationships Between Serum 25OHD Concentration and Bone Metabolism Parameters

We found a weak inverse relationship between serum PTH and 25OHD concentrations that was not significant (Spearman's $\rho = -0.10$; P = .30). Patients with vitamin D deficiency were not more likely to have serum PTH concentration >65 pg/mL than vitamin D-sufficient patients (OR: 0.5; 95% CI: 0.1 to 2.0; P = .33). Measurements of serum 25OHD concentration in our participants were performed using the Nichols Advantage assay (competitive protein-binding assay).[40] Recent studies have found this assay to be inadequate in measuring exogenous sources of vitamin D_2.[41,42] To further investigate whether possible assay-related underrepresentation of serum 25OHD concentrations contributed (especially in patients who reported taking vitamin D supplements) to the lack of a relationship between serum PTH and 25OHD concentration, we performed the analysis separately for participants who reported taking vitamin D supplements and those who did not, and we still did not find a significant relationship (Spearman's ρ (r) = 0.13, P = .57 in those not taking vitamin D supplements; $r = -0.12$, P = .26 in those taking such supplements). To account for effects of puberty, we evaluated the relationship between serum PTH and 25OHD concentrations separately in patients ≤18 years and those >18 years, and we still did not find it to be significant (Spearman's ρ (r) = −0.05, P = .64 in patients ≤18 years; $r = -0.43$, P = .11 in patients >18 years). We also found that serum calcium concentration had a weak inverse

relationship with serum PTH concentration (Spearman's $\rho = -0.17$; $P = .08$) and a weak positive relationship with serum 25OHD concentration (Spearman's $\rho = 0.16$; $P = .09$).

DISCUSSION

Our study identified vitamin D deficiency in 34.6% of children and young adults with IBD. This prevalence of vitamin D deficiency is higher than has been reported previously,[18–20] higher than that among healthy New England adolescents (24.1% ≤15 ng/mL),[38] and similar in patients with CD and UC. Low serum albumin concentration was a significant independent predictor of low serum 25OHD concentration, a finding that has not been reported previously in patients with IBD, to our knowledge. Other risk factors for hypovitaminosis D included winter season, dark skin complexion, low BMI, high ESR, new diagnosis, no vitamin D supplementation, and UGI involvement in patients with CD.

Our finding of higher-than-previously-reported prevalence of vitamin D deficiency among young patients with IBD could be attributed to several factors. Assay-related underrepresentation of serum 25OHD concentrations in subjects taking vitamin D supplements was considered, and is possible, in view of the recently reported Nichols' Advantage assay's inadequacy in measuring exogenous sources of vitamin D_2.[41,42] Nevertheless, our screened subjects were not receiving therapeutic doses of vitamin D_2 (>800 IU of vitamin D_2) when their serum 25OHD concentration was measured. Two of the 3 studies in pediatric subjects with IBD to report vitamin D status used a serum 25OHD concentration <15 ng/mL as the cutoff value for vitamin D deficiency and could have, as a result, underestimated the prevalence of this condition.[19,20] Naturally occurring seasonal variation in serum 25OHD concentrations may also lead to differences in reporting the prevalence of vitamin D deficiency among studies, depending on clustering of sampling during certain seasons. The sampling distribution across seasons was not reported in 2 studies,[19,20] but it was roughly uniform in our study.

We also compared our findings with those of a study performed at our institution, examining the prevalence of vitamin D deficiency (serum 25OHD concentration ≤15 ng/mL) among healthy New England adolescents.[38] This study used the same method and assay for serum 25OHD concentration determination as ours. Prevalence of vitamin D deficiency according to this study was 39.4% during the winter, 44.4% during spring, 12.1% during the summer, and 16.9% during fall. We found a prevalence of vitamin D deficiency of 55.3%, 19.4%, 30.3%, and 28.6% during the respective seasons.

The current literature seems to support the concept that the prevalence of vitamin D insufficiency and deficiency is higher in patients with CD than UC. The only pediatric study to examine vitamin D status of UC patients reports mean serum 25OHD concentrations similar and within normal limits in patients with CD and UC but without using a cutoff value to define vitamin D deficiency.[19] Our findings suggest that pediatric patients with CD and UC do not differ significantly in their vitamin D status and that, after adjusting for other factors, diagnosis becomes less significant. This may be of importance in clinical practice, because it suggests that certain risk factors predispose pediatric patients with IBD to low serum 25OHD concentrations regardless of diagnosis and that both patients with CD and UC may benefit from frequent monitoring of their vitamin D status.

In accordance with findings of other studies in children with IBD,[18] we found a higher prevalence of vitamin D deficiency during winter and among subjects with darker skin complexion and lower serum 25OHD concentrations in patients with CD and UGI involvement. In accordance with findings in adults with IBD,[24] we found a negative relationship between ESR and serum 25OHD concentration and lower serum 25OHD

concentrations in our patients with lower zWt and zBMI. In contrast to findings in adults with IBD,[24] we found lower serum 25OHD concentrations in newly diagnosed patients. Our finding of a positive association of serum 25OHD concentration with vitamin D supplementation has not been observed by other investigators of either adults[18,22] or children[18] with IBD.

IBD could lead to vitamin D deficiency, because patients may have decreased exposure to sunlight, decreased intake, malabsorption, and gastrointestinal loss. Regarding exposure of patients with IBD to sunlight, some investigators have found significantly decreased serum 25OHD concentration in patients with IBD during both winter and summer in the Northern Hemisphere,[23] and others report a tendency toward lower sun exposure in patients with CD compared with healthy controls even in the summer.[27] Decreased oral vitamin D intake in patients with IBD compared with healthy individuals has been neither consistently documented[27] nor linked with low serum 25OHD concentrations.[18,22] Intestinal absorption of vitamin D was found to be normal in the majority of patients with IBD, regardless of the severity of disease.[27,43]

Protein-losing enteropathy frequently complicates the course of IBD[44] resulting in hypoalbuminemia. Vitamin D and its metabolites are bound to plasma vitamin D binding protein (DBP) regardless of their origin (endogenous or exogenous).[3] Only 0.04% of the total 25OHD and 0.4% of the 1,25-hydroxy-vitamin D are encountered as “free” unbound sterols in the circulation.[3] DBP is an α-globulin, which belongs to the albumin superfamily of binding proteins.[45] The loss of albumin and immunoglobulins into the gut lumen is well documented in patients with IBD.[37,46] Loss of DBP, and with it vitamin D, has not been studied in patients with IBD, but it is a likely mechanism.

To our knowledge, we are the first to report albumin concentration as an independent predictor of serum 25OHD concentration in pediatric patients with IBD. Based on the strong relationship between serum 25OHD and albumin concentration, we hypothesize that protein-losing enteropathy is a leading mechanism of hypovitaminosis D. This has important implications for treatment, because both enteral and parenteral supplementation of this vitamin may prove inadequate, at least in the usual dose, and in patients with active disease.

The significance of hypovitaminosis D among pediatric patients with IBD is unclear and deserves further study. In healthy adolescents and adults, serum 25OHD concentration has been negatively correlated with serum PTH concentration.[4,6,38,47] This relationship between serum 25OHD and PTH concentrations has not been consistently reproduced in patients with IBD. In accordance with findings in healthy subjects, some investigators found a negative association of serum 25OHD concentration with serum PTH concentration in IBD patients.[21,31] Others have observed an increased prevalence of secondary hyperparathyroidism only after intestinal resection[25,26,48] and in undernourished patients with CD.[29] In contrast to findings in healthy subjects, serum PTH concentrations similar to those of healthy controls were found in patients with IBD despite their lower serum concentrations of 25OHD,[22,49] and serum PTH and 25OHD concentrations actually lower than those of healthy controls were found by others in patients with IBD.[50] Two studies report PTH status in pediatric patients with IBD. In one of these studies,[19] lower PTH concentrations occurred in patients with CD than in those with UC, despite lower serum 25OHD concentrations. In the other,[20] an increase in serum PTH concentration was seen after treatment of CD. We found no relationship between serum PTH and 25OHD concentrations. This finding could not be explained solely by assay-related underrepresentation of serum 25OHD concentration in subjects taking vitamin D supplements, because a relationship between PTH and 250HD was absent in subjects not taking supplements as well. We speculate that in patients with IBD, bone resorption is

independent of vitamin D deficiency and likely a result of their increased underlying inflammatory state. Adequate supplementation and/or bone resorption probably maintain serum calcium at appropriate concentrations, thus alleviating the occurrence of secondary hyperparathyroidism in these patients, even when they are vitamin D deficient. It remains to be examined whether secondary hyper-parathyroidism will eventually occur if serum 25OHD concentration remains low during a quiescent phase of the disease, when inflammation-induced bone resorption is less likely. This would imply that vitamin D supplementation may be of greater benefit during disease remission.

The relationship between serum 25OHD concentration and BMD is controversial in studies of patients with IBD. Serum 25OHD concentration correlated positively with BMD of the forearm in unselected patients with CD,[26] and lower serum 25OHD concentration correlated significantly with low hip and spine BMD in patients with small intestinal resections.[48] On the other hand, many investigators found that BMD was not related to vitamin D status in either adults[22,25] or children[18] with IBD. Moreover, BMD was found to be low despite normal serum 25OHD concentration in many studies of patients with IBD.[33,34,50,51] We found no significant association between serum 25OHD concentration and zLSBMD among our subjects, although there was a high prevalence of low zLSBMD. We selected a time interval of 6 months before or after BMD measurement to assess the vitamin D status of our patients, because our goal was to capture in a cross-sectional manner a serum 25OHD concentration that would be most representative and reflective of the vitamin D status of the patients around the time of their BMD measurement. Some investigators reported seasonal variation in BMD and bone turnover of the same subjects with loss of bone mass or high bone turnover during the winter months and gain of bone mass or lower bone turnover during the summer months, which could be reflective of seasonal variation in vitamin D status.[5,23] We did not assess BMD and vitamin D status during the same season in our subjects, but we found that mean zLSBMD did not differ between winter/spring and summer/fall, whereas serum 25OHD concentration had a clear seasonal variation. To better evaluate the relationship between vitamin D status and BMD in pediatric patients with IBD, prospective longitudinal studies relating several measurements of serum 25OHD concentration throughout the year with BMD measurements are needed.

The findings in this study must be considered in light of acknowledged limitations. Some limitations stem from the retrospective nature of this study. For example, additional factors that may have influenced vitamin D status in our subjects may have not been considered. Sunlight exposure among our patients was not studied in detail. Nevertheless, seasonal variation was considered and found significant. Dietary vitamin D intake was not measured. However, although the total amount of daily vitamin D intake through diet and supplements is unknown, vitamin D supplementation seems to place the subjects in an advantageous position regarding their vitamin D status, according to our findings. In this study, the number of available patients with UC was lower than that of patients with CD. Nevertheless, reporting vitamin D status and risk factors for hypovitaminosis D separately in these 2 groups of patients was one of the objectives of our study, based on current concepts, now challenged, of their differences in regard to vitamin D status.

CONCLUSIONS

We found a high prevalence of hypovitaminosis D among pediatric patients with IBD, regardless of their diagnosis. Lower 25OHD concentrations may be found among young patients with more active disease (as evidenced by higher ESR), severe disease (as indicated by lower albumin level), those not taking vitamin D supplements, those with suboptimal nutritional status (as indicated by low BMI *z* score), those early in their diagnosis, and those with UGI involvement (in patients with CD). The mechanism of hypovitaminosis D in

patients with IBD is not entirely clear, and further studies will be necessary to elucidate its etiology and implement successful treatment. A primary mechanism could be protein-losing enteropathy. We found no relationship between serum 25OHD concentration and bone density of the lumbar spine and no relationship between serum 25OHD and PTH concentrations. Thus, the significance of hypovitaminosis D for the bone health of young patients with IBD merits further study. We suggest that prospective observational and interventional studies of the vitamin D status be undertaken in pediatric subjects with IBD. Prospective observational studies could confirm the finding that protein-losing enteropathy may be a major mechanism for hypovitaminosis D in this population. Interventional studies could identify the appropriate dosage and timing of vitamin D supplementation for the maintenance of optimal vitamin D stores in this population and the effects of this intervention on bone health. Both types of studies are underway in our center.

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Abbreviations

25OHD	25-hydroxy-vitamin D
BMD	bone mineral density
IBD	inflammatory bowel disease
CD	Crohn disease
UC	ulcerative colitis
UGI	upper gastrointestinal tract
LSBMD	lumbar spine bone mineral density
PTH	parathyroid hormone
ESR	erythrocyte sedimentation rate
DXA	dual-energy x-ray absorptiometry
GCRC	General Clinical Research Center
zLSBMD	*z* score of lumbar spine bone mineral density
zWt	*z* score of weight
zHt	*z* score of height
zBMI	*z* score of BMI
OR	odds ratio
CI	confidence interval
DBP	vitamin D– binding protein

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TABLE 1

Clinical Characteristics and Laboratory Values of the 130 Patients

Characteristic[a]	Value[b]			
	All Patients (*N* = 130)	CD (*N* = 94 [72.3%])	UC (*N* = 36 [27.7%])	CD vs UC *P*[c]
Age, y				
Mean ± SD	15 ±3	15 ±3	14 ±4	
Range	8 to 23	8 to 23	8 to 22	.69
Gender				
Male	67 (51.5)	51 (54.3)	16 (44.4)	
Female	63 (48.5)	43 (45.7)	20 (55.6)	.32
Ethnicity				
White	120 (92.3)	88 (93.6)	32 (88.9)	
Black	6 (4.6)	3 (3.2)	3 (8.3)	
Hispanic	3 (2.3)	3 (3.2)	0	
Other	1 (0.8)	0	1 (2.8)	.36[d]
zHt (*N* = 125)		(*N* = 90)	(*N* = 35)	
Mean ± SD	−0.50 ±1.00	−0.69 ±1.03	−0.01 ±0.76	
Range	−3.36 to 2.13	−3.36 to 1.85	−1.32 to 2.13	.001
zWt (*N* = 129)		(*N* = 93)	(*N* = 36)	
Mean ± SD	−0.12 ±1.25	−0.33 ±1.30	0.42 ±0.95	
Range	−4.22 to 2.47	−4.22 to 2.33	−2.44 to 2.47	.002
zBMI (*N* = 125)		(*N* = 90)	(*N* = 35)	
Mean ± SD	0.13 ±0.19	−0.01 ±1.24	0.50 ±0.96	
Range	−4.86 to 2.44	−4.86 to 2.44	−2.40 to 2.27	.03
zLSBMD				
Mean ± SD	−1.2 ±1.1	−1.3 ±1.2	−1.0 ±1.0	
Range	−4.7 to 2.5	−4.7 to 2.5	−2.7 to 1.4	.10
Disease duration, mo (*N* = 129)		(*N* = 94)	(*N* = 35)	
Mean ± SD	30 ±33	30 ±32	32 ±37	
Range	0 to 157	0 to 147	0 to 157	.72
Lifetime steroids, mg (*N* = 129)		(*N* = 93)	(*N* = 36)	
Mean ± SD	4063 ±5407	3561 ±3985	5361 ±7923	
Range	0 to 38 325	0 to 22 329	0 to 38 325	.09
Intestinal resection (*N* = 129)	13 (10.2)	(*N* = 94)	(*N* = 34)	
		8 (8.5)	5 (14.7)	.30
Albumin				
Mean ± SD	3.9 ±0.6	3.8 ±0.6	4.1 ±0.4	
Range	1.7 to 5.0	1.7 to 5.0	3.0 to 4.9	.02
Hematocrit				
Mean ± SD	37.6 ±3.8	37.3 ±3.9	38.2 ±3.5	
Range	28.0 to 51.0	28.0 to 51.0	30.8 to 46.8	.24

Characteristic[a]	Value[b]			
	All Patients (*N* = 130)	CD (*N* = 94 [72.3%])	UC (*N* = 36 [27.7%])	CD vs UC *P*[c]
ESR (*N* = 128)		(*N* = 92)	(*N* = 36)	
Mean ± SD	20 ±17	23 ±19	12 ±10	
Range	1 to 93	1 to 93	2 to 54	.001

[a] Where applicable, when *N* not specified, assume 130.

[b] Data are given as *n* (%) unless otherwise indicated.

[c] Pearson χ^2 test for dichotomous variables, 2-sample *t* test with equal variances assumed for continuous variables.

[d] *P* value based on comparison between white and all nonwhite subjects.

TABLE 2

Vitamin D Status-Related Values in All Patients

Characteristic	Value[a]			
	All Patients (*N* = 130)	CD (*N* = 94 [72.3%])	UC (*N* = 36 [27.7%])	CD vs UC, *P*[b]
25OHD ≤15	45 (34.6)	36 (38.3)	9 (25)	.16
25OHD ≤8	14 (10.8)	12 (12.8)	2 (5.6)	.25
25OHD, ng/mL		(*N* = 94)	(*N* = 36)	
Mean ± SD	20.9 ± 10.7	20.0 ± 10.3	23.4 ± 11.7	
Range	7.0–56.1	7.0–50.2	7.0–56.1	.10
PTH (*N* = 110), pg/mL		(*N* = 79)	(*N* = 31)	
Mean ± SD	41.4 ± 17.3	42.3 ± 18.3	39.0 ± 14.3	
Range	9.0–106.1	9.0–106.1	20.3–66.1	.38
Ca (*N* = 112)		(*N* = 81)	(*N* = 31)	
Mean ± SD	9.5 ± 0.4	9.4 ± 0.4	9.5 ± 0.3	
Range	7.8–10.4	7.8–10.4	8.9–10.1	.25
Vitamin D supplementation[c]		(*N* = 92)	(*N* = 36)	.18
(*N* = 128)	99 (77.3)	74 (80.4)	25 (69.4)	
Season of 25OHD assessment				
Winter[d]	38 (29.2)	30 (31.9)	8 (22.2)	
Spring	31 (23.8)	20 (21.3)	11 (30.6)	
Summer	33 (25.4)	25 (26.6)	8 (22.2)	
Fall	28 (21.5)	19 (20.2)	9 (25)	.52

Ca indicates serum calcium.

[a] Data are given as *n* (%) unless otherwise indicated.

[b] Pearson χ^2 test for dichotomous variables, Fisher's exact test for nominal variables, 2-sample *t* test with equal variances assumed for continuous variables.

[c] Refers to intake of any form of vitamin D supplement including multivitamins at any time during the 3 months before the 25OHD measurement and not to dietary vitamin D intake. Subjects who reported taking vitamin D supplements were taking between 400 and 800 IU of vitamin D per day in addition to dietary vitamin D.

[d] Winter is from December 22 to March 21; spring, March 22 to June 21; summer, June 22 to September 21; fall, September 22 to December 21.

TABLE 3

Linear Regression for Log (25OHD)

Characteristic	Total Subjects[a]	Simple Regression		Multiple Regression	
		Percent Difference in 25OHD Concentration (95% CI)	*P*	Percent Difference in 25OHD Level (95% CI)	*P*
Diagnosis					
CD	94	Reference		Reference	
UC	36	19.5 (−3.1 to 47.2)	.10	8.9 (−11.9 to 34.6)	.43
Age		−1.6 (−4.4 to 1.2)	.25		
Gender					
Male	67	Reference			
Female	63	6.2 (−12.1 to 28.2)	.53		
Ethnicity					
White	120	52.6 (7.8 to 116.0)	.02	52.5 (8.0 to 115.3)	.02
Other	10	Reference		Reference	
Season					
Winter	38	−33.4 (−45.2 to −19.0)	<.001	−31.4 (−44.0 to −16.1)	<.001
Other	92	Reference		Reference	
Vitamin D supplementation[b]					
Yes	99	31.5 (5.2 to 64.4)	.02	4.8 (−16.1 to 31.0)	.67
No	29	Reference		Reference	
zHt	125	7.8 (−1.9 to 18.4)	.12		
zWt	129	9.1 (1.2 to 17.5)	.02		
zBMI	125	8.6 (0.3 to 17.6)	.04	1.8 (−6.2 to 10.3)	.67
Disease duration, per y	129	3.1 (−0.3 to 6.7)	.08	2.9 (−0.8 to 6.8)	.13
Lifetime steroids, per 1000 mg	129	−0.6 (−2.3 to 1.2)	.50	−1.2 (−3.1 to 0.6)	.19
Resection					
Yes	13	−6.8 (−32.0 to 27.6)	.66	−0.3 (−27.2 to 36.6)	.98
No	116	Reference		Reference	
Albumin		46.8 (26.0 to 71.1)	<.001	32.6 (8.5 to 62.0)	.01
ESR	128	−0.7 (−1.2 to −0.1)	.01	0.0 (−0.6 to 0.6)	.97
Hematocrit		0.1 (−2.3 to 2.6)	.93		

[a] Where applicable, when *N* not specified, assume 130.

[b] Refers to intake of any form of vitamin D supplement including multivitamins at any time during the 3 months before the 25OHD measurement and not to dietary vitamin D intake. Subjects who reported taking vitamin D supplements were taking between 400 and 800 IU of vitamin D per day in addition to dietary vitamin D.