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Prevalence and Risk Factors for Hypovitaminosis D in Young Patients with Inflammatory Bowel Disease: A Retrospective Study

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Abstract

Background and aims—Vitamin D plays an important role in bone homeostasis. Children with inflammatory bowel disease (IBD) are known to have several risk factors for hypovitaminosis D. We aimed to report the prevalence of hypovitaminosis D in this population and risk factors associated with low serum twenty five hydroxy-vitamin D (25OHD) concentration in children with IBD.

Methods—Serum 25OHD concentration of 448 patients with IBD 8 to 22 yrs measured between January 2006 and January 2009 at our Center was recorded via retrospective chart review. Data collected included diagnosis (ulcerative colitis (UC), Crohn disease (CD) and indeterminate colitis (IC)), demographics, serum albumin concentration, erythrocyte sedimentation rate, vitamin D intake, season of measurement and height, and weight. Factors related to serum 25OHD concentration were identified with regression analysis.

Results—Serum 25OHD concentration ≤20 ng/mL (insufficiency) was identified in 64 patients (14.3%) and serum concentration ≤15 ng/mL (deficiency) in 26 (5.8%). Factors associated with lower serum 25OHD concentration were: winter and spring season, dark skin complexion, higher body mass index Z-score, lack of vitamin D supplementation and higher erythrocyte sedimentation rate.

Conclusion—Hypovitaminosis D is prevalent among children and youth, including patients with IBD. Risk factors for deficiency of this vitamin are similar to those in healthy children, with the addition of higher erythrocyte sedimentation rate. Both patients with UC and CD are at risk for hypovitaminosis D.

Keywords

Hypovitaminosis D; Inflammatory Bowel Disease

Introduction

Vitamin D plays an important role in bone metabolism, and also serves as an immunomodulator [1]. Children with inflammatory bowel disease have decreased bone mineral density (BMD) in comparison to healthy peers. The role of vitamin D in improving

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and protecting bone health or improving disease outcomes in children with IBD has not been established, moreover, the lowest vitamin D level which would promote bone health and regulate the immune system has not been defined. Based on rickets prevention, a serum 25OHD concentration > 20 ng/mL has been defined as the level of sufficiency in children [2]. Maintaining sufficient vitamin D levels in children with IBD may be difficult due to malabsorption and other disease-related factors. Direct comparison of the prevalence of vitamin D insufficiency among children with IBD and their healthy peers has not been reported as of yet, although a recent study reported lower vitamin D levels in children with newly diagnosed IBD in comparison to age, sex and ethnicity matched controls [3]. We reported a prevalence of serum 25OHD concentration < 15 ng/mL in 34% of children with IBD in our Center [4]. We report herein the prevalence and risk factors of hypovitaminosis D in children with IBD in a subsequent study of this population.

Methods

Serum 25OHD concentration of patients with IBD, 8 to 22 years, cared for at the Children's Hospital Boston Division of Gastroenterology, was measured as part of their clinical care and these measurements were used for the screening phase of interventional prospective studies in this population involving vitamin D supplementation. The Children's Hospital Institutional Review Board (IRB) approved all phases of these studies including retrospective chart review. We retrospectively recorded all patients' 25OHD serum concentration measured between January 1, 2006 and January 1, 2009. Through a retrospective chart review, we collected information on age, gender, ethnicity, diagnosis of Crohn disease (CD), ulcerative colitis (UC) and indeterminate colitis and vitamin D supplementation in the patients whose 25OHD serum concentration was measured. Serum albumin concentration (g/dL), erythrocyte sedimentation rate (ESR, mm/sec), and patients' height and weight was also recorded if measured within one month from the serum 25OHD concentration measurement. In the case of ESR, measurements were not recorded if through chart review there was sufficient evidence that an elevated value was due to a concurrent illness unrelated to IBD (i.e. upper respiratory infection). For statistical purposes, ethnicity was reported as White or non-White, with African American and Hispanic as non-White. Data on serum albumin concentration and ESR were selectively collected due to previous results from our group linking serum albumin concentration with serum 25OHD concentrations [4]. Weight (Kg) and height (cm) were recorded as reflecting patients' nutritional status. Patients were considered as taking vitamin D supplementation if the clinician's report on the day of the serum 25OHD serum concentration measurement notes regular intake of any supplement containing vitamin D. Serum 25OHD concentration was measured in ng/mL with the DiaSorin Liaison assay, a direct competitive immunochemiluminescent assay that accurately measures both $25OHD_2$ and $25OHD_3$ [5]. ESR and albumin were measured using Excyte-40 automated ESR analyzer (Vital Diagnostics, Lincoln, RI) and the Cobas 6000 chemical analyzer (Roche Diagnostics, Basel, Switzerland) respectively. Height and weight were measured using a Harpenden stadiometer (Veeder-Root counter) (Crymych, UK), and a Scaletronix scale (accuracy 100 g) (White Plains, NY) respectively. BMI as well as weight, height and BMI Z-scores were calculated using the Epi Info nutrition program, version 3.5.3 with the CD 2000 reference. Respective Z-scores for patients older than 20 years were calculated using an age of 20 years.

Serum 25OHD concentration was classified as optimal (> 32ng/mL), sub-optimal (≤32 ng/mL), insufficient (≤20 ng/mL) or deficient (≤15 ng/mL) [1, 6].

Statistical analysis was performed using SPSS 15.0. To evaluate differences between the two major diagnosis groups (CD and UC), a Chi square test, an independent sample t-test or a Mann-Whitney test was performed, depending on the nature and distribution of the data.

Continuous variables were tested for normality using the Shapiro-Wilk test. If normality was not fulfilled, non parametric tests were used. Data for patients with indeterminate colitis were not reported separately, due to their small number. The influence of various factors on serum 25OHD concentration was analyzed through simple regression analysis. For the later, the dependent variable was the serum 25OHD concentration and the independent variables were ethnicity, season of measurement (a dichotomous value; winter and spring versus summer and fall), height, weight and BMI Z-score, diagnosis, vitamin D supplementation (when available) and ESR and serum albumin concentration if measured within 1 month of serum 25OHD concentration measurement. Since serum 25OHD concentration was not normally distributed, the values were log transformed. We then applied multiple regression analysis to examine the effect of diagnosis, ESR and albumin on serum 25OHD concentration, independently of confounding by other factors in this cohort. BMI Z-score, ethnicity, season of measurement and vitamin D intake were entered in the regression model as known factors independently affecting serum 25OHD concentration in healthy individuals. Serum albumin concentration, ESR and diagnosis were then entered one by one and their regression coefficient as well as significance of their relationship to serum 25OHD concentration was tabulated after this adjustment. The difference in log-transformed serum 25OHD was converted to difference in percentage units using the following formula: 100 % x $[10^{\text{change in log serum 25OHD concentration}} - 1]$ = percent change. A p-value ≤0.05 was set to indicate statistical significance.

Results

A total of 448 individual patients had their serum 25OHD concentration measured at least once during the specified study interval. In this group, 288 patients (64.3%) carried the diagnosis of CD, 143 (31.9%) that of UC and 17 (3.8%) carried the diagnosis of indeterminate colitis. Further characteristics are shown in Table 1. Of note is that more patients with CD had their serum 25OHD concentration measured during the summer and fall months than the winter and spring, whereas patients with UC had their serum 25OHD concentration measured evenly throughout the year. Mean weight, height and BMI Z-score was lower, and mean ESR was higher in patients with CD. Patients with UC had lower mean serum 25OHD concentration than patients with CD, and vitamin D deficiency was more prevalent among patients with UC (Table 1).

In simple regression, serum 25OHD concentration was found to be 10.9% higher in summer and fall than in winter and spring (confidence intervals 3.6, 17.4, p = 0.004), 22% higher in “white” patients than patients with darker skin complexion (confidence intervals 13.9, 29.6, p < 0.001), 18.9% higher among patients who were taking vitamin D supplements (confidence intervals 6.7, 32.7, p = 0.002), 10.9% higher for every g/dL increase in serum albumin concentration (confidence intervals 1.6, 21.1, p = 0.02), 3.4% lower for every 1 SD increase in weight Z-score (confidence intervals −7.1, −0.5, p = 0.03), and 11.3% lower in patients with UC than CD (confidence intervals −18.3, −3.8, p = 0.004).

After adjustment for ethnicity, season of measurement, BMI Z-score and vitamin D intake, higher ESR was independently significantly associated with lower serum 25OHD (3.8% lower for every 10 mm/sec of rise in ESR, confidence intervals −7.1, −0.5, p = 0.03). Serum albumin’s significance level was 0.06 after adjustment (serum 25OHD concentration 13.2% higher for every g/dL increase in serum albumin concentration, confidence intervals −0.7, 28.8), and diagnosis lost its significance as a predictor of serum 25OHD level after adjustment (serum 25OHD concentration 8.2% lower in UC than in CD patients, confidence intervals −17.8, 2.3, p = 0.12).

Conclusion and discussion

In this sample from a tertiary care center in Boston, MA (42° N), 58.3% of pediatric patients with IBD had sub-optimal serum 25OHD concentration (25OHD ≤32 ng/mL), 14.3% had serum 25OHD level at or below 20 ng/mL, and 5.8% at or below 15 ng/mL. Although the prevalence of vitamin D insufficiency (25OHD < 20 ng/mL) in our study does not appear to be higher than that encountered among healthy children, even at lower latitudes in the U.S. [7], the racial distribution differences among the reporting studies cannot allow for direct comparisons and generalizations. As expected, serum 25OHD concentration showed a strong relationship with skin complexion. Kumar et al. found a prevalence of serum 25OHD concentration <15 ng/mL in 9% of healthy children throughout the United States [8], which is higher than that encountered in our study population. This discrepancy can be explained by the fact that the percentage of children with darker skin complexion is higher in the group of healthy children examined in the study above than in our study (about 32% vs 16.7% in our study population), reflecting the racial distribution of the diagnosis of IBD in the general population. Another study performed by Gordon et al. among healthy adolescents in the Boston area showed a prevalence of serum 25OHD concentration <15 ng/mL of 24%. In that study of healthy youth, subjects of white race comprised only 16% of the sample [9].

In a previous study conducted in our Center, we reported serum 25OHD concentration < 15 ng/mL in 34% of children with IBD, with racial distribution similar to that of the current study [4]. This significant difference could be explained by the difference in assays used for measurement of serum 25OHD concentration in the two studies: in our previous study, we used the Nichols competitive binding assay, whereas in our current study we used the Diasorin Liaison assay. The later measures accurately both vitamin D_2 and D_3, whereas the former may not detect vitamin D_2 levels as accurately, thus underestimating its contribution to the serum 25OHD concentration. Of note is that the percentage of patients taking vitamin D supplementation was actually higher in our previous study compared to the present study (77% vs. 57%).

BMI Z-score was negatively associated with serum 25OHD level in our study. This finding is in agreement with findings in healthy children [10]. Sequestration of vitamin D in adipose tissue and its resulting decreased bioavailability in other tissues is a leading hypothesis for this observation. Doses of vitamin D for both treatment of vitamin D deficiency and as supplementation for maintenance of optimal vitamin D stores may have to be higher, to account for increased adipose tissue in both healthy children and children with IBD. However, the threshold above which adipose tissue interferes with vitamin D bioavailability and appropriate dosing of vitamin D to overcome this have not been defined as of yet.

ESR is used as a surrogate marker of intestinal inflammation in IBD. It was found to be independently associated with lower 25OHD serum level in both our current and previous studies [4]. Intestinal inflammation could theoretically affect vitamin D status through impaired absorption and/or loss of circulating protein-bound vitamin D through the inflamed intestinal mucosa. Serum albumin concentration is a surrogate marker of protein-losing enteropathy, but also of nutritional status. Serum albumin concentration's association with serum 25OHD concentration did not reach significance in our study when adjusted for other factors ($p = 0.06$) -including nutritional status representatives such as BMI Z-score - but it may have if the number of patients was larger. Clearly, further study is needed to define the mechanism through which intestinal inflammation affects vitamin D homeostasis.

Limitations of this study include its retrospective design, the lack of comparable healthy controls, and the non-systematic collection of data such as vitamin D intake in all patients. In addition, data related to disease severity and course were limited in the present study.

Vitamin D may play an important role in bone health and control of inflammation in children with IBD. However, direct comparison of the prevalence of hypovitaminosis D in this population and in healthy children with similar racial distribution has not been undertaken. Our present study highlights the fact that hypovitaminosis D is prevalent among children with IBD. Risk factors for hypovitaminosis D in this population are similar to those identified in healthy children; darker skin complexion, winter season, higher BMI Z-score reflecting increased adipose tissue mass, and lack of vitamin D supplementation. In addition, higher ESR is associated with lower vitamin D levels in this population. The decision to screen vitamin D status in children with IBD should not be dependent on diagnosis, since both children with CD or UC appear to be at risk for this problem. Further studies are needed to a) directly compare healthy children to children with IBD in terms of their vitamin D status, b) uncover the effect of intestinal inflammation on vitamin D homeostasis and c) quantify the effect of adipose tissue on vitamin D bioavailability and define appropriate dosing of vitamin D based on this effect.

Abbreviations

IBD	inflammatory bowel disease
25OHD	twenty fine hydroxy-vitamin D
UC	ulcerative colitis
CD	Crohn disease
IC	indeterminate colitis
BMD	bone mineral density

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Table 1

Patients' characteristics

	Mean ± SD OR N (%) (range)			
	All patients (N=448) [1]	**CD (N=288)**	**UC (N=143)**	**CD vs. UC p**
Age, yrs	15.7 ± 3.2 (8 to 22)	15.9 ± 3.1 (8 to 22)	15.4 ± 3.3 (8 to 22)	.1
Gender				
Male	235 (52.5)	161 (55.9)	65 (45.5)	
Female	213 (47.5)	127 (44.1)	78 (54.5)	.04
Ethnicity				
White	373 (83.3)	239 (83.0)	121 (84.6)	
Other	75 (16.7)	49 (17.0)	22 (15.4)	.67
Height Z-score	−0.38 ±1.02 (−4.6 to 2.46) N=442[1]	−0.47 ±1.02 (−4.6 to 2.46) N=283	−0.16 ±1.02 (−3.44 to 2.33) N=142	0.003
Weight Z-score	−0.04 ±1.2 (−8.75 to 2.83) N=444[1]	−0.14 ±1.24 (−8.75 to 2.83) N=285	0.21 ±1.1 (−4 to 2.72) N=142	0.004
BMI Z-score	0.14 ±1.09 (−5.33 to 2.52) N=442[1]	0.06 ±1.11 (−5.33 to 2.52) N=283	0.31 ±1.05 (−2.87 to 2.45) N=142	0.02
Serum 25OHD levels (ng/mL)	31 ± 12 (7 to 86)	33 ± 12 (7 to 86)	29 ± 11 (7 to 69)	.006
Sub-optimal serum (25OHD≤32 ng/mL)	262 (58.5)	160 (55.6)	91 (63.6)	.1
Vitamin D insufficiency (25OHD≤20 ng/mL)	64 (14.3)	31 (10.8)	28 (19.6)	.01
Vitamin D deficiency (25OHD≤15 ng/mL)	26 (5.8)	12 (4.2)	12 (8.4)	.08
Vitamin Supplementation	124 (57.1) (N=217) [1]	85 (59.4)	38 (58.5)	.89
Season of measurement				
Winter (Dec 21–Mar 20)	98 (21.9)	56 (19.5)	39 (27.3)	
Spring (Mar 21–Jun 20)	83 (18.6)	45 (15.7)	33 (23.1)	
Summer (Jun 21–Sep 20)	117 (26.2)	80 (27.9)	32 (22.4)	
Fall (Sep 21 Dec–20)	149 (33.2)	106 (36.9)	39 (27.3)	.03
Serum albumin concentration (g/dL)	4.1 ± 0.5 (1.6 to 5.1) (N=391) [1]	4.1 ± 0.5 (1.6 to 5) N=246	4.2 ± 0.4 (2.3 to 5.1) N=131	0.15
ESR (mm/sec)	16.3 ±15.2 (1 to 122)	18 ±16.1 (1 to 122)	12.8 ±12.6 (1 to 84)	<0.001

	Mean ± SD OR N (%) (range)			
	All patients (N=448) [1]	**CD (N=288)**	**UC (N=143)**	**CD vs. UC p**
	N=430 [1]	N=275	N=139	

SD: standard deviation, CD: Crohn's disease, UC: ulcerative colitis, BMI: body mass index, ESR: erythrocyte sedimentation rate

[1] Number includes indeterminate colitis patients