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The nondietary determinants of vitamin D status in pediatric inflammatory bowel disease

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ABSTRACT

Objectives: The aim of this study was to investigate the relationships between 25-hydroxy vitamin D (25[OH]D) and markers of vitamin D status in inflammatory bowel disease (IBD).
Methods: We conducted a retrospective case–control study of 59 pediatric patients with IBD (age 16.4 ± 2.2 y) and 116 controls (age 14.6 ± 4.4 y), to investigate the association between 25(OH)D and albuminemia for protein-losing enteropathy (PLE) and hepatic dysfunction; alanine transaminase (ALT) for hepatic inflammation; erythrocyte sedimentation rate (ESR) for intestinal inflammation; body mass index (BMI) for adiposity; seasons and skin pigmentation for insolation. Vitamin D deficiency was defined as 25(OH)D < 50 nmol/L; abnormal liver enzyme by ALT >40 U/L; overweight status by BMI of ≥85th but <95th percentile, and obesity by BMI ≥95th percentile. Seasons were categorized as summer, winter, spring, and fall.
Results: Patients with IBD had a higher prevalence of vitamin D deficiency (42.4% versus 26.7%; $P = 0.04$), elevated ALT (16.9% versus 2.6%; $P < 0.001$), and lower albumin (41.1 ± 4.8 versus 45.1 ± 3.8; $P < 0.001$) than controls. In both the IBD cohort and controls, 25(OH)D was highest in summer and lowest in winter, and significantly higher in white than in non-white patients. ESR varied significantly with 25(OH)D ($R^2 = 0.24$; $\beta = -0.32$; $P = 0.010$), and only patients with IBD with elevated ESR had lower 25(OH)D than controls (49.5 ± 25.2 versus 65.3 ± 28.0 nmol/L; $P = 0.045$).
Conclusion: Intestinal inflammation, not the loss of albumin-bound vitamin D in the gut, is the primary intestinal determinant of vitamin D status in IBD. The extraintestinal determinants are seasons and skin pigmentation, but not adiposity and hepatic inflammation.

Introduction

The mechanism of vitamin D deficiency in inflammatory bowel disease (IBD) is not clear. Uncontrolled studies examining the determinants of vitamin D status in IBD identified serum albumin concentration as both a surrogate marker of protein-losing enteropathy (PLE) [1] and a stronger predictor of vitamin D status in IBD than body mass index (BMI) *z*-score, season, skin pigmentation, and erythrocyte sedimentation rate (ESR) [2]. This has led to the hypothesis that hypoalbuminemia (from PLE), not malabsorption, is the primary mechanism for hypovitaminosis D in IBD [2,3]. This hypovitaminosis D is believed to result from the loss of vitamin D bound to vitamin D–binding protein into the gut lumen.

However, because hepatic inflammation can also result in hypoalbuminemia, a comprehensive examination of the relationship between hypoalbuminemia and vitamin D status in IBD necessitates an evaluation of hepatic inflammation. Furthermore, a crucial step in vitamin D metabolism, the hydroxylation of vitamin D at the 25 position to form 25-hydroxy vitamin D (25[OH]D), occurs in the liver [4] and pathologic states that impair this hydroxylation step may also result in vitamin D deficiency. Additionally, hepatobiliary disorders are common in IBD [5]; and some of the medications employed in the management of IBD are hepatotoxic and could result in hepatic dysfunction.

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Additionally, the role of intestinal inflammation on vitamin D status in IBD has not been fully examined. Traditionally, ESR serves as a marker of the degree of intestinal inflammation in IBD [1], but its relationship with 25(OH)D has not been adequately evaluated [1,2].

Similarly, although adiposity is associated with vitamin D deficiency in healthy individuals [6,7], this association is unclear in IBD. This is crucial because, despite the strong association between IBD and growth retardation, obesity and overweight have been reported in IBD [8] at rates of 20% and 30%, respectively [9].

Finally, the role of insolation, the exposure of the skin to solar radiation, as assessed by season and skin pigmentation has not been fully investigated in IBD [10,11]. Whereas one study reported that darkly pigmented individuals with IBD had lower vitamin D concentration than a light-pigmented cohort [10], another study found no difference in 25(OH)D between black children with IBD and their black controls [11]. Two uncontrolled studies [12,13] investigating the effect of seasons on vitamin D status in IBD reported lower serum 25(OH)D concentration in winter than in summer.

The aim of this study was to investigate the relationships between 25(OH)D and markers of non-dietary determinants of vitamin D status in IBD using a case–control study design. Its hypothesis is that intestinal inflammation, not protein-losing enteropathy, is the principal determinant of vitamin D status in IBD.

Participants and methods

Ethics statement

The study protocol was approved by the University of Massachusetts Institutional Review Board. All patient records and information were anonymized and deidentified before analysis.

Participants

We reviewed the medical records of children and adolescents ages 2 to 20 y with a confirmed diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) between January 1, 2007 and June 30, 2013 at the Children's Medical Center Database of the UMassMemorial Medical Center in Worcester, Massachusetts.

Study participants (N = 59; 31 males) were included if they had a confirmed diagnosis of CD or UC. The diagnosis of CD and UC was established by a combination of standard clinical, endoscopic, and radiographic criteria, as documented at the time of diagnosis [14]. Routinely measured laboratory analytes—serum 25(OH)D, alanine transaminase (ALT), albumin, and ESR—were available for all participants. These analytes were drawn on the same day for each patient, except in a few cases (n = 9) in which they were obtained within 1 mo of vitamin D estimation.

A group of healthy children and adolescents from the general pediatric clinics of the Children's Medical Center served as controls (n = 116; 49 males). The control group was randomly selected using a systematic sampling scheme. For this method, the list of control participants was alphabetized, and then every fifth individual was selected for inclusion. Participants were included in the control group if they had no diagnosis of CD or UC, but had serum 25(OH)D, ALT, and albumin drawn during a clinic visit between January 1, 2007 and June 30, 2013. All analyte measurements were obtained on the same day as part of a routine comprehensive metabolic panel.

Patients were excluded from this study if they had a diagnosis of chronic liver disease; disease affecting calcium or vitamin D metabolism; malabsorption syndrome other than IBD; vitamin D or calcium supplementation before the date of 25(OH)D measurement; or steroid therapy for the management of any disease other than IBD. Pregnant or lactating women were also excluded. Of the 76 patients with IBD who met the inclusion criteria, 17 were excluded based on the aforementioned exclusion criteria. Fifty-nine individuals were included in the analysis.

The ages of both the study participants and the controls were determined by the date of 25(OH)D measurement. The duration of disease was designated as the interval from the date of endoscopic diagnosis of IBD to the date of 25(OH)D measurement. The percentages of participants from the various ethnic/racial groups for the control group were as follows: non-Hispanic white (NHW) 75%, black 8%, white Hispanic 5%, multiethnicity 5%, and unknown 4%. Similarly, the percentages from the various ethnic/racial groups for the IBD groups were: NHW 85%, black 3%, white Hispanic 3%, multiethnicity 3%, and unknown 5%.

Because vitamin D status could vary with sunlight exposure and the seasons, we categorized each participant's date of vitamin D draw according to the seasons as follows: fall (September 22–December 21), winter (December 22–March 21), spring (March 22–June 21), and summer (June 22–September 21) [15].

Anthropometry

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain Ltd, Crymych, Dyfed, UK), which was calibrated daily. Weight was measured to the nearest 0.1 kg using an upright scale. BMI was derived using the formula weight/height^2 (kg/m^2) and expressed as SD score (SDS) for age and sex based on National Center for Health Statistics data [16]. Overweight was defined as BMI of ≥85th but <95th percentile, whereas obesity was defined as a BMI of ≥95th percentile for age and sex.

Assay

Serum 25(OH)D concentration was analyzed using 25-hydroxy chemiluminescent immunoassay (DiaSorin Liaison; Stillwater, MN, USA), which has a 100% cross-reactivity with both metabolites of 25(OH)D, namely 25(OH)D_2 and 25(OH)D_3, and thus measures total serum 25(OH)D content. Its functional sensitivity is 10 nmol/L, and its intra- and interassay coefficients of variation are 5% and 8.2%, respectively. Vitamin D status was defined using 25(OH)D values based on criteria by The Endocrine Society Clinical Practice Guideline as follows: vitamin D deficiency <20 ng/mL (50 nmol/L), insufficiency 20 to 29.9 ng/mL (50–74.5 nmol/L), and sufficiency ≥30 ng/mL (75 nmol/L) [17], which is similar to the classification of vitamin D status by the American Academy of Pediatrics and the Institutes of Medicine criteria, which denote vitamin D deficiency as 25(OH)D < 50 nmol/L and sufficiency as 25(OH)D > 50 nmol/L [18,19].

Albumin concentrations were measured in a Roche/Hitachi 917 chemistry analyzer (Roche Diagnostic Corporation, Indianapolis, IN, USA) according to standard protocol. ESR was measured using ESR analyzer Vesmatic 20 (Clinical Data, Inc., Smithfield, RI, USA) according to standard protocol. ALT was measured using the Beckman Coulter AU System ALT procedure (Beckman Coulter, Inc., Brea, CA, USA).

Statistical analyses

Statistical analyses were performed using the SPSS Predictive Analytics SoftWare v.21 (IBM Corporation, Armonk, NY, USA). Means and SDs were calculated for descriptive summary statistics and 25(OH)D measurements. Multivariate and univariate comparisons on anthropometrics, 25(OH)D, and other variables were conducted using analysis of variance (ANOVA) and two-tailed Student's *t* test, respectively. Height, weight, and BMI data were expressed as *z*-scores. Race, sex proportionality, and seasons of blood draw were compared using Fisher's exact test. The values for ALT, albumin, and ESR were logarithmically transformed before analysis to approximate normality. Simple and multiple-linear regression models, describing the relationships between anthropometric and biochemical parameters, were specified. Data were expressed as mean ± SD.

Results

Comparison of characteristics of IBD group versus controls

There were no differences in sex, height, race, season of 25(OH)D measurement, mean serum 25(OH)D, or ALT between the IBD group and controls (Table 1). Participants with IBD were older ($P < 0.001$), had lower BMI *z*-score ($P = 0.04$) and albumin concentration ($P < 0.001$), and had a significantly higher prevalence of vitamin D deficiency (42.4% versus 26.7%; $P = 0.04$) and elevated ALT (16.9% versus 2.6%; $P < 0.001$) than controls.

Comparison of characteristics of patients with UC versus CD

There were no significant differences in age, sex, weight, BMI, disease duration, or season of vitamin D measurement between participants with UC (n = 19) or CD (n = 40). Participants with CD were non-significantly shorter than the UC patients ($P = 0.05$), and there was no difference in serum 25(OH)D concentration between the groups (53.3 ± 25.4 nmol/L versus