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Short communication

Is vitamin D deficiency a feature of pediatric celiac disease?

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Abstract

Background: Celiac disease (CD) is an autoimmune enteropathy characterized by villus atrophy and malabsorption of essential nutrients. Vitamin D deficiency has been described in autoimmune diseases, but its status in prepubertal children with CD has not been adequately studied.
Objective: To determine the vitamin D status of prepubertal children with CD.
Study design: A retrospective study of prepubertal children aged 3–12 years with CD (n=24) who were compared to prepubertal, non-CD children of the same age (n=50). Children were included in the study if they had a diagnosis of CD by intestinal biopsy, and were not on a gluten-free diet (GFD). Patients were excluded if they had diseases of calcium or vitamin D metabolism, or were receiving calcium or vitamin D supplementation or had other autoimmune diseases. All subjects had their serum 25-hydroxyvitamin D [25(OH)D] level measured.
Results: There was no difference in 25(OH)D level between the CD and non-CD children (27.58±9.91 vs. 26.20±10.45, p=0.59). However, when the patients were subdivided into obese and non-obese groups, the non-obese CD patients had a significantly higher 25(OH)D level than the obese normal children (28.39±10.26 vs. 21.58±5.67, p=0.009). In contrast, there was no difference in 25(OH)D level between non-obese CD patients and non-obese normal children (28.39±10.26 vs. 30.64±12.08, p=0.52). The season of 25(OH)D measurement was not a significant confounder (p=0.7).
Conclusions: Our data showed no difference in 25(OH)D levels between normal children and those with CD when adjusted for body mass index.

Keywords: celiac disease; children; prepubertal status; vitamin D.

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Introduction

Celiac disease (CD) is an autoimmune enteropathy that affects 0.5–1% of the population (1). It is characterized by villus atrophy and malabsorption of essential nutrients. The pathogenesis of CD is based on a combination of genetic and environmental factors (2). The most important predisposing genetic factors to CD are HLA-DQ2 and HLA-DQ8 molecules (3). There is a 70% concordance for CD in monozygotic twins (2). Environmental factors, such as the time of initial exposure of intestinal epithelium to gluten (4), as well as the duration of gluten exposure are also associated with the development of CD (5).

Gluten is a protein component in wheat, rye and barley. The toxicity associated with these proteins is related to glutamine and proline-rich amino acid sequences (2). An immune response, mostly within the lamina propria, leads to the release of tissue transglutaminase from inflamed cells (2). Tissue transglutaminase is an intracellular enzyme that can interact with glutamine and proline-rich proteins, such as those in gluten (2). These interactions can generate new antigens that are targeted by immunoglobulin A fraction in patients who are genetically predisposed to develop CD. Tissue transglutaminase enzyme, an autoantigen in CD (6) deamidates gluten peptides leading to increased immunoreactivity of the gluten peptides (7). The small bowel damage from activated CD 8+ cells is characterized histologically by an invasion of lymphocytes into the epithelium and lamina propria, progression to crypt hyperplasia, and finally to blunting of intestinal villi (2). Resolution of these intestinal lesions can occur after the removal of the inciting proteins from the susceptible individual's diet (8, 9). Untreated CD, however, is associated with malnutrition in 67% of patients (10). Interestingly, obesity has been reported in children with CD at a prevalence rate of 5% (11).

The role of intestinal epithelial damage on vitamin D absorption in prepubertal children with CD has not been fully studied. Vitamin D receptors are present in the crypts of CD intestine, and it is unclear whether the intestinal inflammation of CD leads to malabsorption of fat-soluble vitamins, and consequent vitamin D deficiency (12). Vitamin D deficiency has been reported in related autoimmune diseases, such as type 1 diabetes mellitus and chronic lymphocytic thyroiditis (13, 14), which are frequently seen in patients with CD (14). Some investigators have speculated that the intestinal damage in CD could result in vitamin D malabsorption and vitamin D deficiency (9, 10). Lerner et al (3) studied two cohorts of patients with CD living in two sunny countries, Israel and Spain, and found that serum concentrations of vitamin D is negatively correlated with age, but not with the degrees of intestinal damage. However, the vitamin D metabolism in prepubertal children with CD in cold climates has not been fully studied. This is important because even though children

in both cold and sunny climates may have a similar degree of villus atrophy, the increased exposure to ultraviolet radiation in sunny countries could easily lead to normal vitamin D levels in children in contrast to children living in colder climates with limited exposure to ultraviolet radiation.

Therefore, to bridge this knowledge gap, we designed this study with the primary aim of determining whether vitamin D insufficiency is a feature of CD in prepubertal children living in cold climates along 42°N. Our hypothesis was that CD children would have low vitamin D levels compared to healthy children. To examine this hypothesis we conducted a retrospective chart review of children with CD who had 25(OH)D measured, and compared this group to a cohort of healthy prepubertal children who participated in a prospective cross-sectional study on the role of vitamin D metabolism on bone mineral content (clinical trial identifier NCT00756899).

Study participants

We reviewed the medical records of prepubertal children aged 3–12 years with CD at the Children's Medical Center of the Umass Memorial Medical Center between 2008 and 2011. The study protocol was approved by the University of Massachusetts Institutional Review Board. Study subjects (n=24; 15 females and nine males) were included if they had a diagnosis of CD, had 25(OH)D level measured at diagnosis, were not on gluten-free diet (GFD), and were not taking vitamin D or calcium supplementation. Patients were excluded if they had diseases of calcium or vitamin D metabolism or had other autoimmune diseases. Diagnosis of CD was based upon upper gastrointestinal biopsies consistent with CD clinical presentation. Age was determined by the date of 25(OH)D measurement. Subjects were categorized into non-obese and obese categories, using a body mass index (BMI) of >95th percentile to define obesity (15).

A group of 50 age-matched healthy prepubertal children who participated in a cross-sectional study entitled 'The Relationship between Vitamin D Deficiency and Low Bone Mineral Content in Children', ClinicalTrials.gov Identifier: NCT00756899, at the Children's Medical Center of the Umass Memorial Medical Center, served as normal controls. All subjects in the control group were prepubertal, had no diagnosis of CD, and were not on vitamin D or calcium supplementation. They had no medical diseases affecting calcium or vitamin D metabolism. Their age was determined by the date of 25(OH)D measurement. This group consisted of 25 obese and 25 non-obese subjects.

Anthropometry

Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Holtain Ltd, Crymych, Dyfed, UK). 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 standard deviation score (SDS) for age and gender based on National Center for Health Statistics (NCHS) data (16).

Assays

The 25(OH)D was assayed by chemiluminescence immunoassay which has 100% cross-reactivity with both vitamin D_2 (the plant-derived form of vitamin D called ergocalciferol) and D_3 (the animal derived form known as cholecalciferol). The immunoassay detects total body 25(OH)D content. Its functional sensitivity is 4 ng/mL (10 nmol/L), and its *intra-* and *inter*-assay coefficients of variation are 5% and 8.2%, respectively. Vitamin D deficiency was defined as a 25(OH)D level of <15 ng/mL, (37.5 nmol/L), vitamin D insufficiency as vitamin D level of 15–20 ng/mL, (37.5–50 nmol/L), and vitamin D sufficiency as 25(OH)D of >20,100 ng/mL, (50–250 nmol/L) based on Pediatric Endocrine Society guidelines (17).

Statistics

Statistical analyses were performed using the SPSS Predictive Analytics SoftWare version19 (IBM Corporation, Somers, NY, USA). Means and standard deviations were calculated for descriptive summary statistics. Anthropometrics and 25(OH) D levels were compared using Student's t-test. Seasons were compared using Fisher's exact test. BMI was expressed as a standard deviation score (SDS).

Results

The baseline characteristics of the study patients and controls are shown in Table 1. There was no difference in mean 25(OH)D level between the CD and non-CD children (27.58±9.91 vs. 26.20±10.45, p=0.59). However, when the patients were subdivided into obese and non-obese groups, the non-obese CD patients had a significantly higher mean 25(OH)D level than the obese normal children (28.39±10.26 vs. 21.58±5.67, p=0.009) (Figure 1). In contrast, there was no difference in mean 25(OH)D level between non-obese CD patients and non-obese normal children (28.39±10.26 vs. 30.64±12.08, p=0.52). Similarly, there was no difference in BMI SDS between non-obese CD patients and non-obese normal children (–0.03±1.28 vs. 0.03±1.12, p=0.87). Mean BMI SDS differed significantly between obese normal children and non-obese normal children (2.54±0.87 vs. 0.03±1.12 p<0.001); and also between obese normal children and non-obese CD patients (2.54±0.87 vs. –0.03±1.28 p<0.001). The seasonality of 25(OH)D measurement was not a significant confounder (p=0.70).

Discussion

We found no difference in mean 25(OH)D levels between normal children and those with CD when adjusted for BMI. We also found that obese children in general had lower vitamin D levels compared to non-obese children.

Our finding is similar to other reports on vitamin D metabolism in CD (3, 9). Lerner et al (3) conducted a transcontinental study involving groups of children and adults with

Table 1 Comparison of the characteristics of children with celiac disease and those of normal children.

Parameters	Celiac disease patients			Normal controls		
Number	All 24	Obese 6	Non-obese 18	All 50	Obese 25	Non-obese 25
Age, year	9.42±2.80	10.31±2.61	9.12±2.87	8.02±2.66	8.48±2.55	7.56±2.73
Sex, males	9	2	7	29	16	13
Height SDS	–0.64±1.32	–0.87±1.97	–0.56±1.10	0.21±1.71	0.96±1.51	–0.55±1.57
Weight SDS	0.06±1.45	1.43±0.63	–0.39±1.36	1.08±1.96	2.55±1.04	–0.03±1.12
BMI SDS	0.47±1.42	1.97±0.27	–0.03±1.28	1.29±1.61	2.54±0.87	0.03±1.12
25(OH)D, ng/mL	27.58±9.91	25.17±9.17	28.39±10.26	26.20±10.45	21.58±5.67	30.64±12.08
Seasons (summer+autumn)	11	4	7	17	8	9

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; SDS, standard deviation score.

CD to determine the effect of CD on vitamin D metabolism. They found no evidence of vitamin D deficiency in their pediatric patients. In contrast, they found significant vitamin D deficiency in their adult population. They explained that this discrepancy could be caused by the fact that children with CD have increased dietary intake of vitamin D, are routinely supplemented with vitamin D in the first year of life, have more exposure to sunlight, and are more compliant with a gluten-free diet compared to adult CD patients. Thus, despite the malabsorptive state in CD, vitamin D deficiency is not a feature of pediatric CD as vitamin D status may be unrelated to the degree of small bowel injury in CD (9). A possible reason for the lack of vitamin D deficiency in children with CD is that a majority of the hormone is produced in the skin upon exposure to ultraviolet radiation (18). Therefore, body stores might depend more on endogenous production rather than gastrointestinal absorption.

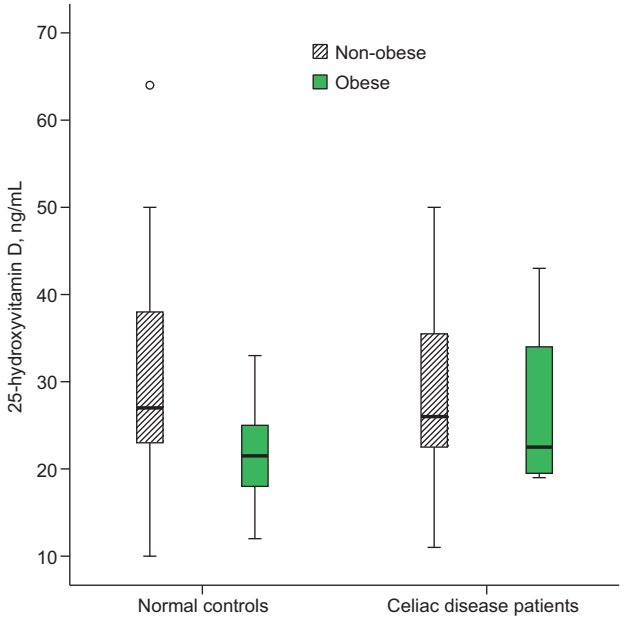

Figure 1 Box plots of the comparison of serum concentrations of 25-hydroxyvitamin D in patients with celiac disease and normal controls stratified by body mass index.

Our finding that obese children had lower vitamin D levels compared to non-obese children is consistent with previous reports on the relationship between 25(OH)D and BMI (19–22).The proposed reasons for vitamin D deficiency in the obese state include sequestration of vitamin D in excess body fat, negative feedback from an elevated 1-25-dihydroxyvitamin D level, poor diet, or an avoidance of sunlight (20–22).

One of the limitations of our study is its cross-sectional design, which makes it difficult to establish temporality in 25(OH)D levels. Secondly, our results cannot be generalized because our patients were all residing in central Massachusetts, located at 42°N, a geographical zone that receives insufficient amounts of ultraviolet radiation in the winter months for adequate skin synthesis of vitamin D. However, the blood samples for the study parameters were collected at different seasons of the year. We also had a smaller sample size for the CD patients compared to non-CD cohort. For example, we had only six obese patients with CD. Such a sample size would be inadequate to detect subtle differences between the groups and could have resulted in type 2 error. However, the proportion of obese patients with CD in our cohort is consistent with the 5% prevalence rate of obesity in the pediatric CD population (11). In contrast, we had a representative number of patients in the non-obese groups for the CD and non-CD cohorts to accurately assess the effects of CD on vitamin D metabolism in this subset of patients. This group of patients was of primary interest for this study because we specifically wanted to exclude the influence of obesity on vitamin D metabolism. The strengths of this study include the fact that we studied only prepubertal children, thus eliminating the effects of hormonal fluctuations associated with pubertal maturation on vitamin D metabolism. We also employed a representative group of control subjects in both the obese and non-obese cohorts. Finally, we provided a much-needed balance to Lerner's study (3) by investigating the vitamin D profiles of children with CD residing in cold climates.

In conclusion, our data show that vitamin D deficiency is not a feature of CD in prepubertal children living in cold climates. This is consistent with an earlier study in sunny climates which showed normal vitamin D levels in children with CD. Therefore, children with CD do not require aggressive vitamin D supplementation.

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