25-Hydroxyvitamin D Concentrations in Children with Crohn's Disease Supplemented with Either 2000 or 400 IU Daily for 6 Months: A Randomized Controlled Study

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Objectives To assess vitamin D status of pediatric patients with Crohn's disease (CD) and to compare their serum 25-hydroxyvitamin D (s-25OHD) with established cutoffs and assess whether 6 months of supplementation with 2000 IU/d, vs 400 IU/d, would reduce the group prevalence of vitamin D below these cutoffs.

Study design Subjects 8-18 years (n = 83) with quiescent CD were randomized to either 400 or 2000 IU vitamin D_3/d for 6 months.

Results Baseline mean ± SD s-25OHD was 24 ± 8 ng/mL; 13 subjects (16%) had an s-25OHD <16 ng/mL, 27 (33%) < 20 ng/mL, and 65 (79%) < 30 ng/mL. There was no significant difference between groups in achieving the cutoffs of 16 ng/mL or 20 ng/mL at 6 months; however, only 35% of the 400 IU group achieved the greater cutoff of 30 ng/mL compared with 74% in the 2000 IU group ($P < .001$). Baseline adjusted mean s-25OHD concentrations at 6 months were 9.6 ng/mL (95% CI 6.0-13.2, $P < .001$) greater in the 2000 IU than the 400 IU group. Disease activity was not affected by supplement dose. Few subjects exceeded safety marker cutoffs, and this did not differ by dose.

Conclusions At baseline, a high proportion of patients had a mean s-25OHD >20 ng/mL. 2000 IU vitamin D_3/d is more effective in raising s-25OHD concentrations to > 30 ng/mL in children with CD than 400 IU/d, but both treatments were equally effective at achieving 16 or 20 ng/mL. *(J Pediatr 2014;164:860-5)*.

In children, Crohn's disease (CD) can result in impaired growth, delayed puberty, and a poor quality of life.[1,2] Low vitamin D status, based on low serum 25-hydroxyvitamin D (s-25OHD) concentrations, has been described in some studies of children with CD.[3] Low bone mineral density is also a common manifestation of the disease in children and adults compared with healthy control subjects.[4-8] Although low bone mineral density has not been attributed to dietary vitamin D deficiency,[4] but rather to the inflammatory processes, as a nutrient essential for bone health, attaining adequate vitamin D status in children with CD is important.

In addition to its role in bone health it is hypothesized that vitamin D may play a role in the development or severity of CD through its immunomodulatory effects.[9-11] Rates of CD are greater at northern latitudes, potentially because of less sunlight exposure leading to lesser levels of vitamin D.[12] Moreover, the rates of CD increase when people who live near the equator migrate to countries at greater latitudes.[13] Finally, in an interleukin-10 knockout mouse model of spontaneous enterocolitis, vitamin D deficiency is associated with increased intestinal inflammation and increased mortality.[14] Conversely, vitamin D supplementation in these mice ameliorates intestinal inflammation.[14]

Jørgensen et al[15] reported a trend towards a reduced rate of relapse in adults with inactive CD supplemented with 1200 IU/d of vitamin D compared with placebo (13% vs 29%, $P = .06$). Patients in the treatment arm achieved mean s-25OHD concentrations of almost 40 ng/mL; it has been suggested that s-25OHD levels need to be >30 ng/mL to fully exert extraskeletal effects.[16]

In a randomized controlled study in a pediatric population age 5-21 years (n = 71), Pappa et al[17] compared the increase in s-25OHD concentrations among 3 short-term vitamin D supplemental regimens in patients with either CD or ulcerative colitis. During the 6-week study, patients receiving 2000 IU/d vitamin D_3 (n = 24) compared with 2000 IU/d vitamin D_2 (n = 24) achieved greater s-25OHD (32

CD	Crohn's disease
CV%	Coefficient of variation
ESR	Erythrocyte sedimentation rate
FFQ	Food Frequency Questionnaire
ITT	Intent to treat
PCDAI	Pediatric Crohn's Disease Activity Index
RDA	Recommended dietary allowance
s-25OHD	Serum 25-hydroxyvitamin D

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vs 26 ng/mL) and were less likely to have levels ≤20 ng/mL (25% vs 38%). A number of questions still need to be addressed. First, would a lower dose of vitamin D_3 be sufficient to achieve a desired status target? Many of the patients (n = 427) screened for the study by Pappa et al[17] were subsequently excluded, presumably many for having a s-25OHD >20 ng/mL. Would less vitamin D be required to achieve a desirable cutoff for those with greater baseline s-25OHD?

Our first aim was to assess vitamin D status in a cohort of pediatric patients with CD and to compare their s-25OHD to recently recommended cutoffs: 16 ng/mL (a serum level analogous to the estimated average requirement[18]); 20 ng/mL (a serum level thought to meet or exceed the needs of most individuals[18]); and 30 ng/mL (recommended by some groups for achieving the nonskeletal benefits of vitamin D[16]). We also sought to assess whether 6 months of supplementation of vitamin D_3 with 2000 IU/d, vs a control dose of 400 IU/d, would reduce the group prevalence of vitamin D inadequacy (<16 ng/mL), and/or the proportion of the group achieving cutoffs of 20 and 30 ng/mL. Finally we aimed to determine whether there was any difference in disease activity between groups, as measured by the Pediatric Crohn's Disease Activity Index (PCDAI).[19]

Methods

The study protocol was conducted in 2 Canadian health centers, the McMaster Children's Hospital and the British Columbia Children's Hospital. Children and adolescents with quiescent CD ages 8-18 years old were eligible to participate. Individuals were excluded if they had been taking corticosteroids within the preceding 6 weeks, or if they were taking a vitamin D–containing supplement with >1000 IU/d. Initial contact with potential subjects was made by a written letter to families. The study was approved by the University of British Columbia Children's and Women's Health Centre of British Columbia Research Ethics Board and the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board. Patients were screened by an attending pediatric gastroenterologist to determine disease quiescence, followed by signing informed consent/assent with a research staff and initiation of the first study visit.

A double-blind, randomized controlled study design was used for this supplementation trial, initiated November 2010 and concluded February 2012. Subjects were randomized at baseline in a 1:1 allocation to either a 400 or 2000 IU/d vitamin D_3 supplement dose. The study consisted of 3 study visits, one at enrollment, one at 3 months, and one at the study end point of 6 months. Study compliance was assessed by weighing leftover supplement bottles at each follow-up visit. At baseline, subject age, ethnicity, CD medication, and supplement use was recorded. Subjects were asked to discontinue any previous vitamin D–containing supplements. A specially designed multivitamin, not containing vitamin D, was offered to all study subjects. Clinic nurses measured subjects' height and weight, and blood and urine samples were collected by hospital laboratory or nursing staff. Patients' disease activity was assessed and scored by the responsible gastroenterologist, using the PCDAI.[19] The PCDAI score is based on a compilation of the patient's reported history and physical and biochemical assessments. Generally, a total score of less than or equal to 10 signifies the patient has quiescent disease, a score of 11-30 signifies mild disease, and a score 31-100 signifies moderate/severe disease.[20]

Supplements were produced by Natural Factors (Coquitlam, British Columbia, Canada) and tested both internally and externally for dose reliability. A control dose of 400 IU/d vitamin D_3 was chosen because the use of a placebo could be considered unethical in this population and because many patients already consumed 400 IU of vitamin D_3 per day as part of a multivitamin. At the time of study design, the experimental dose of 2000 IU/d was the tolerable upper intake level for daily vitamin D consumption in children,[21] although it has since been increased to 3000 IU in children ages 4-8 and to 4000 IU in children 9 years and older.[18]

Subjects and research staff were blinded to supplement doses, which were coded by lot number. Lot numbers were assigned randomly to a sequential study subject identification number by a statistician.

At the 3-month study visit, subjects, aided by their parents where appropriate, were asked to complete a validated Food Frequency Questionnaire (FFQ) to assess their dietary intake of vitamin D in the previous month. Developed by Wu et al,[22] the FFQ has been validated in young Canadian adults of diverse ancestry and found to correlate well with a 7-day food diary ($r = 0.529$, $P < .001$).

Subjects were asked to provide a mid-stream spot urine sample and nonfasting blood sample via venipuncture at each study visit. Serum and urine were stored at −80°C until analysis. All s-25OHD were analyzed with the DiaSorin LIAISON competitive chemiluminescence immunoassay (DiaSorin Inc, Stillwater, Minnesota), at McGill University in the School of Dietetics and Human Nutrition. The laboratory participates in and is certified by the Vitamin D External Quality Assessment Scheme, an external quality control program for 25OHD measurement. Accuracy for Level 1 (SRM 972 Lot 968e 7.1 ± 0.2 ng/mL) Standard Reference Material (National Institute of Standards and Technology, US Department of Commerce, Washington, District of Columbia) was 97.0 ± 5.4% across 7 assays with an interkit coefficient of variation (CV%) of 5.8%. The interkit CV% for the high (31.3-66.8 ng/mL) and low (8.0-21.2 ng/mL) kit controls were 7.2% and 6.9%, respectively. Interkit CV% for 5 samples measured in triplicate across kits was 2.7 ± 1.7%. All other analyses were completed by standardized laboratory procedures at the respective hospital laboratories. These included safety measures of serum calcium and phosphate, urinary calcium, and creatinine as well as inflammatory markers serum C-reactive protein and erythrocyte sedimentation rate (ESR).

In a previous cross-sectional assessment of 39 Canadian children with CD, mean s-25OHD concentrations were approximately 26.8 ng/mL (SD 10.8 ng/mL).[23] Another