# Treatment of Vitamin D Insufficiency in Children and Adolescents with Inflammatory Bowel Disease: A Randomized Clinical Trial Comparing Three Regimens

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**Context:** Vitamin D insufficiency [serum 25-hydroxyvitamin D (25OHD) concentration less than 20 ng/ml] is prevalent among children with inflammatory bowel disease (IBD), and its treatment has not been studied.

**Objective:** The aim of this study was to compare the efficacy and safety of three vitamin D repletion regimens.

**Design and Setting:** We conducted a randomized, controlled clinical trial from November 2007 to June 2010 at the Clinical and Translational Study Unit of Children's Hospital Boston. The study was not blinded to participants and investigators.

**Patients:** Eligibility criteria included diagnosis of IBD, age 5–21, and serum 25OHD concentration below 20 ng/ml. Seventy-one patients enrolled, 61 completed the trial, and two withdrew due to adverse events.

**Intervention:** Patients received orally for 6 wk: vitamin $D_2$, 2,000 IU daily (arm A, control); vitamin $D_3$, 2,000 IU daily (arm B); vitamin $D_2$, 50,000 IU weekly (arm C); and an age-appropriate calcium supplement.

**Main Outcome Measure:** We measured the change in serum 25OHD concentration (Δ25OHD) (ng/ml). Secondary outcomes included change in serum intact PTH concentration (ΔPTH) (pg/ml) and the adverse event occurrence rate.

**Results:** After 6 wk, Δ25OHD ± SE was: 9.3 ± 1.8 (arm A); 16.4 ± 2.0 (arm B); 25.4 ± 2.5 (arm C); $P$ (A *vs.* C) = 0.0004; $P$ (A *vs.* B) = 0.03. ΔPTH ± SE was −5.6 ± 5.5 (arm A); −0.1 ± 4.2 (arm B); −4.4 ± 3.9 (arm C); $P$ = 0.57. No participant experienced hypercalcemia or hyperphosphatemia, and the prevalence of hypercalciuria did not differ among arms at follow-up.

**Conclusions:** Oral doses of 2,000 IU vitamin $D_3$ daily and 50,000 IU vitamin $D_2$ weekly for 6 wk are superior to 2,000 IU vitamin $D_2$ daily for 6 wk in raising serum 25OHD concentration and are well-tolerated among children and adolescents with IBD. The change in serum PTH concentration did not differ among arms. **(*J Clin Endocrinol Metab* 97: 2134–2142, 2012)**

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Abbreviations: BMI, Body mass index; CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IQR, interquartile range; 25OHD, 25-hydroxyvitamin D; UC, ulcerative colitis; UCa, urinary calcium; Ucr, urinary creatinine.

Hypovitaminosis D is prevalent and may be encountered more frequently among children with inflammatory bowel disease (IBD) compared with healthy peers (1–4). Vitamin D exerts anabolic effects on bone (5) and may play a role in improving bone health in children with IBD (6). This vitamin is also involved in the regulation of the immune system (7), and it may play a role in the pathogenesis of IBD (8) and as an adjunct to treatment.

In pediatric populations, serum 25-hydroxyvitamin D (25OHD) concentration greater than 20 ng/ml is considered "sufficient" based on rickets prevention (9). However, studies in adults have shown that PTH levels begin to plateau and intestinal calcium transport is maximized when serum 25OHD concentration is at least 32 ng/ml (10, 11). Mechanisms responsible for suboptimal vitamin D status that may be amplified in children and adolescents with IBD include: decreased vitamin D intake from foods and supplements, decreased intestinal absorption, and increased loss through an inflamed intestine. Studies have identified upper gastrointestinal involvement, disease severity, and compromised nutritional status as risk factors for hypovitaminosis D in this population (1, 3).

Guidelines for the treatment of vitamin D insufficiency (serum 25OHD concentration <20 ng/ml) in healthy children include the use of a wide range of cumulative vitamin D doses (84,000 to 600,000 IU) and recommend the higher doses for adolescents (9). There are no studies examining the efficacy and safety of any regimen for the treatment of vitamin D insufficiency in children with IBD. We hypothesized that: 1) doses in the higher end of the proposed spectrum are needed for this purpose, given that this disease preferentially afflicts adolescents, and disease-specific factors may reduce the bioavailability of vitamin D; and 2) vitamin $D_3$ is more efficacious than vitamin $D_2$, in accordance with the literature (12, 13).

We conducted a clinical trial to compare the efficacy and safety of three regimens—two testing vitamin $D_2$ and one testing vitamin $D_3$—in raising serum 25OHD concentration in young patients with IBD and vitamin D insufficiency.

## Subjects and Methods

### Participants

Inclusion criteria were: diagnosis of IBD, age 5 to 21 yr, and serum 25OHD concentration of 20 ng/ml or less within 8 wk of enrollment. Exclusion criteria were: liver or kidney failure, ongoing therapy with anticonvulsants metabolized through cytochrome P-450, pregnancy, inability to take oral medications, attendance at a tanning salon once weekly or more, and receiving treatment for hypovitaminosis D. The study protocol was approved by the Children's Hospital Boston (CHB) Internal Review Board. Informed consent was obtained from participants if they were at least 18 yr old or from their guardians if they were younger. All participants younger than 18 yr signed assent.

### Interventions

Participants were randomized to one of three treatment arms for 6 wk: arm A, 2,000 IU of oral vitamin $D_2$ daily; arm B, 2,000 IU of oral vitamin $D_3$ daily; or arm C, 50,000 IU of oral vitamin $D_2$ once weekly. All regimens included daily oral elemental calcium intake (1,200 mg if ≥11 yr old and 800 mg if <11 yr old). Vitamin $D_2$ was provided as a liquid preparation (8,000 IU/ml) (calciferol drops; Schwarz Pharma, Inc., Milwaukee, WI). The dosage was 0.25 ml daily for arm A and 6.25 ml weekly for arm C. Vitamin $D_3$ was provided as a liquid preparation (400 IU per drop) (Bio-D-Mulsion; Biotics Research Corporation, Rosenberg, TX). The dosage was 5 drops daily.

Participants were asked to complete two visits in the CHB Clinical and Translational Study Unit: enrollment/randomization, and follow-up 6 to 8 wk later. Visits included anthropometric measurements, questionnaire administration, a physical examination, and nutritional assessment by research nutritionists. Study medications were provided to participants after randomization at the initial study visit. The investigators demonstrated their correct use to participants.

### Randomization

Randomization was based on a permuted block design with one stratum. Upon enrollment of a participant, the investigators provided a number from a list to the research pharmacist who assigned a treatment based on a master randomization assignment list, available to him only. The "next patient assignment" was concealed from the investigators.

### Blinding

Participants and investigators were not blinded to treatment assignment for safety reasons. We believe that this limitation was offset by the fact that the primary outcome was objective.

### Outcomes

The primary outcome was the pre-post treatment change in serum 25OHD concentration. Secondary outcomes included change in serum PTH concentration and any posttreatment potential harm from vitamin D, including: hypercalciuria (urine calcium:creatinine ratio ≥0.20), hyperphosphatemia (serum phosphorus concentration >5.7 mg/ml), hypercalcemia (serum calcium concentration >10.5 mg/dl), and serum 25OHD concentration > 88 ng/ml because this concentration has been accepted as the threshold below which vitamin D intoxication has not been reported (14).

### Sample size

Because neither a target level nor the increment of serum 25OHD concentration in response to a specific dose of vitamin D has been established in children with IBD, we sought to compare the effect of three widely used theapeutic vitamin D doses on serum 25OHD concentration. Power analysis demonstrated that a sample size of 20 participants per arm would provide 80% power to detect a change in serum 25OHD concentration in either of the two experimental arms (B and C) that is at least 53% greater than the change in the control arm (A). This was a rea-

sonable expectation because arm C vitamin $D_2$ dose is 250% greater than arm A, and vitamin $D_3$ is three times more potent than vitamin $D_2$ at the same dose.

Total enrollment was increased to 71 to ensure that at least 60 participants had a primary outcome.

## Data

### *Anthropometric data*

Height and weight were measured using a Harpenden Stadiometer (Holtain Limited, Crymych, UK) and a Scaletronix Scale (Scaletronix, White Plains, NY) respectively. Body mass index (BMI) and the Z-scores of all measurements were calculated using Epi Info software, version 3.5.3, with Centers for Disease Control 2000 reference (http://wwwn.cdc.gov/epiinfo/). For participants who were older than 20 yr, Z-scores were calculated using an age of 20 yr.

### *Disease-related data*

Diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) was established using standard criteria (15). Disease activity was reported using the Pediatric Crohn's Disease Activity Index (PCDAI) (16) if less than 20 yr of age and the Crohn's Disease Activity Index (CDAI) (17) otherwise; and for UC, the Pediatric Ulcerative Colitis Activity Index (PUCAI) (18) if less than 19 yr of age, and the Kozarek score (19) otherwise. Participants were classified as having "moderate/severe disease" (PCDAI $\geq$ 30, CDAI $\geq$ 220, Kozarek $>$ 6, PUCAI $\geq$ 35), "mild disease" (10 $\leq$ PCDAI $<$ 30, 150 $\leq$ CDAI $<$ 220, 4 $\leq$ Kozarek $\leq$ 6, 10 $\leq$ PUCAI $\leq$ 34), or "inactive disease" (PCDAI $<$ 10, CDAI $<$ 150, Kozarek $<$ 4, PUCAI $<$ 10) (17, 18, 20). Chart review and interviews were used to report upper gastrointestinal involvement (granulomas in the esophagus, stomach, or duodenum), complications (strictures, fistulae, abscesses) in participants with CD, use of immunomodulators and biologics, glucocorticoid exposure (expressed in milligrams as prednisone equivalents), IBD-related hospitalization and surgery, comorbidity, extraintestinal manifestations of IBD, and enteral supplementation.

### *Nutritional data and lifestyle exposure to vitamin D*

Nutrient and supplement intake was evaluated using a prospective 3-d food record developed by CHB research nutritionists. The record contained instructions for completion including portion measurements. The completed record was returned at the follow-up visit. Nutrient analysis was performed using the Food Processor SQL software, version 10.6.0 (ESHA Research, Salem, OR). Travel experience, use of sunscreen, and exposure to UV radiation through artificial tanning and outdoors dwelling were reported through a specifically developed questionnaire to identify the effect of differential exposure to sunlight on the primary outcome. The relevant questionnaire is provided as Supplemental Data (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

### *Laboratory data*

Serum concentrations of 25OHD (ng/ml), PTH (pg/ml), calcium (mg/dl), phosphorus (mg/dl), C-reactive protein (CRP; mg/dl), albumin (g/dl), and erythrocyte sedimentation rate (ESR; mm/h), as well as spot measurements of urinary calcium (UCa; mg/dl) and creatinine (Ucr; mg/dl) were obtained at each visit. Participants were asked to abstain from ingestion of dairy products and calcium supplements the day of the study.

Serum 25OHD concentration was measured using the DiaSorin Liaison, a two-site chemiluminescence immunoassay that accurately detects both $25OHD_2$ and $25OHD_3$, at ARUP Laboratories (Salt Lake City, UT). The intra- and interassay precision is 7.3–9 and 8.6–10.0%, respectively. The sensitivity is less than 7.0 ng/ml.

Serum PTH concentration was measured using the Access Chemiluminescent Immunoassay (Beckman Coulter, Fullerton, CA) at the Harvard Catalyst Central Laboratory (Brigham & Women's Hospital, Boston, MA). The sensitivity of the assay is 1 pg/ml. The intra- and interassay variation is 1.6–2.6 and 2.8–5.8%, respectively.

ESR was measured using the Excyte-10 automated ESR analyzer (Vital Diagnostics, Lincoln, RI); serum albumin, CRP,

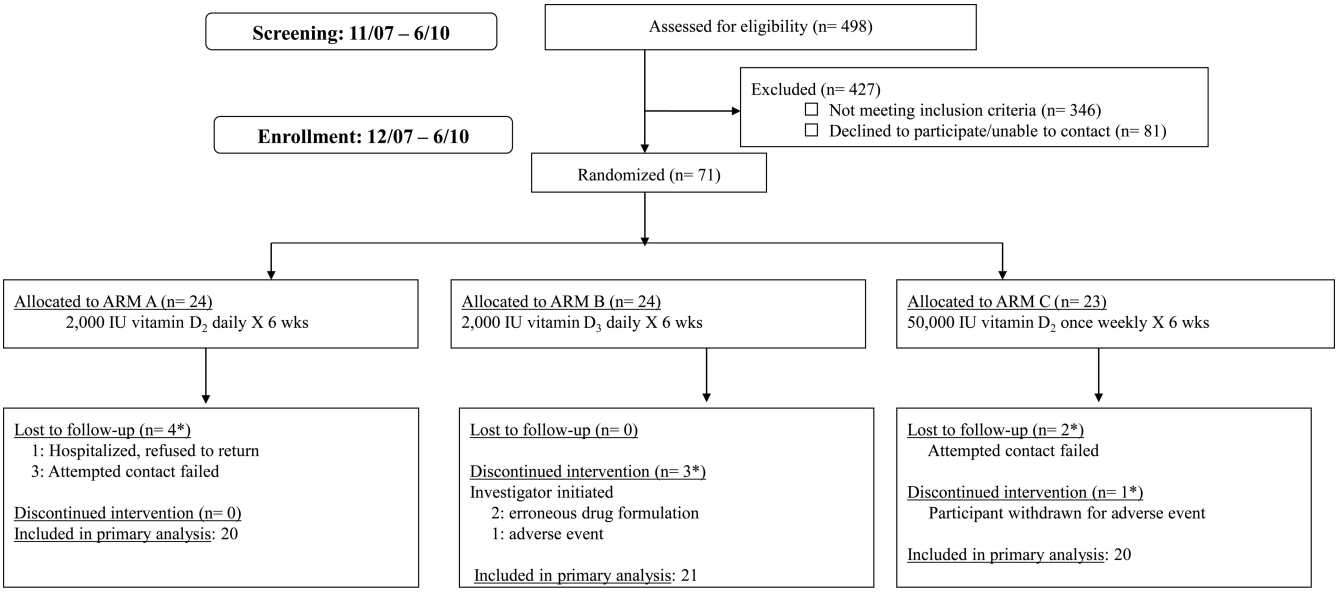


**FIG. 1.** Study overview.

calcium, and phosphorus, as well as UCa and Ucr were measured using the Cobas 6000 chemical analyzer (Roche Diagnostics, Basel, Switzerland). These tests were performed at Laboratory Corporation of America (LabCorp, Raritan, NJ).

### *Compliance*

Compliance of participants to study medications was evaluated through study-specific questionnaires and was expressed as percentage of the required doses of the study medication taken.

### *Adverse events*

Data regarding clinical adverse events were collected using study-specific questionnaires. Participants' reports of adverse events were both volunteered and elicited—responding to a list of adverse events associated with vitamin D toxicity (Calciferol drops package insert, 2007). These included: constipation, drowsiness, bone and muscle pain, xerostomia, headache, polyuria, thirst, headache, heart rhythm irregularity, loss of appetite, nausea, vomiting, fatigue, metallic taste, pruritus, increased sensitivity to light, and calcium deposits. All participants reporting adverse events were analyzed, regardless of withdrawal status. Adverse event severity and relation to study medication was assessed.

## Statistical methods

Data and outcomes were analyzed based on the intention to treat principle. The analysis of the primary outcome was restricted to participants with non-missing outcomes at both enrollment and follow-up. *P* values of the two primary comparisons (A *vs.* B and A *vs.* C) were Bonferroni adjusted so that the

**TABLE 1.** Subject characteristics at and before enrollment (n = 71)

| Characteristics | No. missing in arms A, B, C | Treatment arm A | B | C | *P*[a] |
|---|---|---|---|---|---|
| Dose | | 2,000 IU $D_2$ daily | 2,000 IU $D_3$ daily | 50,000 IU $D_2$ weekly | |
| n | | 24 | 24 | 23 | |
| **At enrollment** | | | | | |
| Season at enrollment: winter/spring (*vs.* summer/fall)[b] | 0, 0, 0 | 83% | 75% | 91% | 0.36 |
| Subject characteristics | | | | | |
| Male | 0, 0, 0 | 58% | 42% | 61% | 0.35 |
| Non-Hispanic White | 0, 0, 0 | 63% | 63% | 57% | 0.89 |
| Age (yr) | 0, 0, 0 | 15.9 ± 3.0 | 14.7 ± 3.5 | 16.3 ± 3.2 | 0.23 |
| BMI Z-score | 2, 3, 0 | 0.47 ± 1.4 | 0.34 ± 0.98 | 0.40 ± 1.12 | 0.94 |
| Disease characteristics | | | | | |
| Diagnosis | 0, 0, 0 | | | | 0.62 |
| CD | | 50% | 58% | 65% | |
| UC | | 46% | 33% | 35% | |
| IC | | 4% | 8% | 0% | |
| Months since diagnosis | 3, 5, 0 | 33 (9–45) | 7 (1–44) | 33 (14–50) | 0.24 |
| Current disease activity[c] | 0, 0, 0 | | | | 0.29 |
| Inactive | | 54% | 54% | 78% | |
| Mild | | 38% | 42% | 22% | |
| Moderate/severe | | 8% | 4% | 0% | |
| Lifetime treatment history | | | | | |
| Glucocorticoids (mg) | 2, 1, 2 | 2, 145 (700–4, 000) | 1, 280 (440–2, 880) | 2, 240 (0–3, 858) | 0.59 |
| Biologics | 0, 0, 0 | 38% | 25% | 35% | 0.62 |
| Immonumodulators | 0, 0, 1 | 75% | 63% | 65% | 0.62 |
| Enteral supplementation | 0, 0, 0 | 29% | 25% | 17% | 0.63 |
| Laboratory values | | | | | |
| ESR (mm/h) | 0, 0, 0 | 14 (10–19) | 13 (6–17) | 11 (5–22) | 0.50 |
| CRP (mg/dl) | 0, 0, 0 | 0.2 (0.1–1.3) | 0.1 (0.1–0.2) | 0.4 (0.1–0.6) | 0.03 |
| Albumin (g/dl) | 1, 1, 0 | 4.1 ± 0.4 | 4.3 ± 0.3 | 4.2 ± 0.3 | 0.11 |
| Serum Ca (mg/dl) | 0, 2, 1 | 9.5 ± 0.5 | 9.6 ± 0.3 | 9.4 ± 0.3 | 0.21 |
| Serum P (mg/dl) | 1, 2, 2 | 4.2 ± 0.8 | 4.0 ± 0.8 | 3.9 ± 0.7 | 0.61 |
| Serum Mg (mg/dl) | 0, 2, 2 | 2.1 (2.1–2.2) | 2.2 (2.0–2.2) | 2.1 (2.1–2.3) | 0.98 |
| UCa:Ucr ≥0.2 | 2, 5, 0 | 32% | 11% | 4% | 0.04 |
| Nutrition | | | | | |
| Vitamin D intake (IU/d) | 1, 0, 2 | 193 (76–423) | 157 (82–518) | 355 (124–587) | 0.44 |
| Ca intake (mg/d) | 4, 2, 0 | 821 ± 390 | 887 ± 329 | 941 ± 427 | 0.60 |
| **Within 1 month before enrollment** | | | | | |
| Outdoor exposure (h/wk) | 0, 0, 0 | 5.3 (2.8–11.0) | 3.0 (2.0–5.3) | 3.0 (1.5–21.0) | 0.32 |
| Sunscreen use | 0, 0, 0 | 13% | 4% | 22% | 0.17 |

Data are expressed as percentage, mean ± SD, or median (IQR). IC, Indeterminate colitis; Ca, calcium; P, phosphorus; Mg, magnesium.

[a] From Pearson $\chi^2$, Fisher exact test, ANOVA, or Kruskal-Wallis test, as appropriate for the distribution of the outcome.

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

[c] Subjects with indeterminate colitis were handled as CD or UC according to phenotype.

overall type I error rate was controlled at 5%. A significance level of 0.05 was used for all other statistical testing. Data were analyzed using SPSS 16.0 (IBM Corporation, Armonk, NY) and SAS (SAS/STAT software, version 9.2; SAS Institute, Cary, NC).

Participants' characteristics and laboratory values, as well as withdrawal and loss to follow-up status, were tabulated and compared among the three arms at baseline and at the end of the trial. Adverse events including occurrence, timing, severity, and relationship to study medication were compared among the three arms. The dose of vitamin D per kilogram of body weight was calculated for each participant and reported as a mean value for each arm.

Changes in serum 25OHD and PTH concentration were compared between arms A and B and arms A and C with the Student's *t* test or the Mann-Whitney test, depending on the distribution of the data. For all other continuous outcomes, one-way ANOVA was used if the residuals to such models were normally distributed; otherwise, the Kruskal-Wallis test was used. For categorical variables, the $\chi^2$ test was used.

## Results

Between November 2007 and June 2010, 498 patients with IBD had their serum 25OHD concentrations measured as part of their clinical care in the outpatient gastroenterology clinics or the inpatient units of Children's Hospital Boston. Seventy-one of 152 patients who qualified for participation enrolled in the trial (Fig. 1).

Table 1 presents demographic and clinical characteristics for all 71 participants at or before enrollment. No differences were found in season of enrollment, baseline demographics and anthropometrics, disease status/treatment, and vitamin D and calcium intake. CRP and prevalence of hypercalciuria (UCa:Ucr ≥0.2) were marginally higher in arms C and A, respectively. Similar comparisons for data obtained at the follow-up visit were not statistically significant (data not shown; see Supplemental Table 1), with the exception of daily vitamin D intake aside from vitamin D provided by the study [arm A, 214 (36–287) IU; arm B, 240 (27–718) IU; arm C, 400 (250–529) IU; $P = 0.05$). One participant in arm A attended a 10-min tanning session. Thirteen subjects crossed seasonal categories from baseline to follow-up (11 from Winter/Spring to Summer/Fall, and two vice versa), and the proportion crossing did not differ between arms ($P = 0.93$).

The mean change in serum 25OHD and PTH concentration from baseline to follow-up is shown in Table 2 and Fig. 2. It was 9.3 ± 1.8 ng/ml in arm A, 16.4 ± 2.0 ng/ml in arm B, and 25.4 ± 2.5 ng/ml in arm C. Arms B and C experienced statistically greater mean changes than arm A (Bonferroni adjusted $P = 0.03$ and $P = 0.0004$, respectively). Both arms B and C were 95% successful in raising serum 25OHD concentration above 20 ng/ml; however, only 38% of subjects in arm B and 75% in arm C raised

**TABLE 2.** Primary and secondary outcomes

| Outcome measures | No. missing in arms A, B, C | Treatment arms | | | *P*[a] | | |
|---|---|---|---|---|---|---|---|
| | | A | B | C | Overall | A *vs.* C | A *vs.* B |
| n | | 2,000 IU $D_2$ daily 24 | 2,000 IU $D_3$ daily 24 | 50,000 IU $D_2$ weekly 23 | | | |
| Vitamin D dose (IU/kg) | 0, 1, 3 | 1,543 ± 89 | 1,773 ± 142 | 5,430 ± 439 | <0.0001 | | |
| 25 OHD (ng/ml) | | | | | | | |
| Baseline | 0, 0, 0 | 16.1 ± 1.0 | 14.7 ± 0.8 | 15.3 ± 1.0 | 0.59 | | |
| Follow-up | 4, 3, 3 | 25.7 ± 2.2 | 31.5 ± 1.9 | 40.8 ± 2.6 | 0.0001 | | |
| Change | 4, 3, 3 | 9.3 ± 1.8 | 16.4 ± 2.0 | 25.4 ± 2.5 | <0.0001 | 0.0004[b] | 0.03[b] |
| >20 ng/ml at follow-up | 4, 3, 3 | 15 (75%) | 20 (95%) | 19 (95%) | 0.14 | | |
| >32 ng/ml at follow-up | 4, 3, 3 | 5 (25%) | 8 (38%) | 15 (75%) | 0.004 | | |
| PTH (pg/ml) | | | | | | | |
| Baseline | 1, 4, 3 | 39.7 ± 5.7 | 37.4 ± 3.5 | 40.4 ± 4.6 | 0.87 | | |
| Follow-up | 5, 4, 7 | 40.2 ± 3.3 | 37.3 ± 3.9 | 39.6 ± 5.5 | 0.70 | | |
| Change | 6, 7, 9 | −5.6 ± 5.5 | −0.1 ± 4.2 | −4.4 ± 3.9 | 0.57 | 1.00[b] | 1.00[b] |
| Electrolytes/UCa | | | | | | | |
| Change in serum calcium | 4, 3, 4 | −0.1 ± 0.1 | 0.0 ± 0.1 | 0.0 ± 0.1 | 0.66 | | |
| Change in serum phosphorus | 5, 3, 6 | −0.1 ± 0.1 | 0.0 ± 0.2 | 0.2 ± 0.2 | 0.54 | | |
| UCa:Ucr ≥0.2 at follow-up | 7, 1, 10 | 2 (12%) | 4 (17%) | 2 (15%) | 1.00 | | |

Data are expressed as mean ± SE or number (percentage).

[a] From Pearson $\chi^2$, Fisher exact test, ANOVA, Kruskal-Wallis, Student's *t* test, or Mann-Whitney test, as appropriate for the distribution of the outcome and the number of parameters tested.

[b] The *P* values were from Mann-Whitney tests and were Bonferroni adjusted.

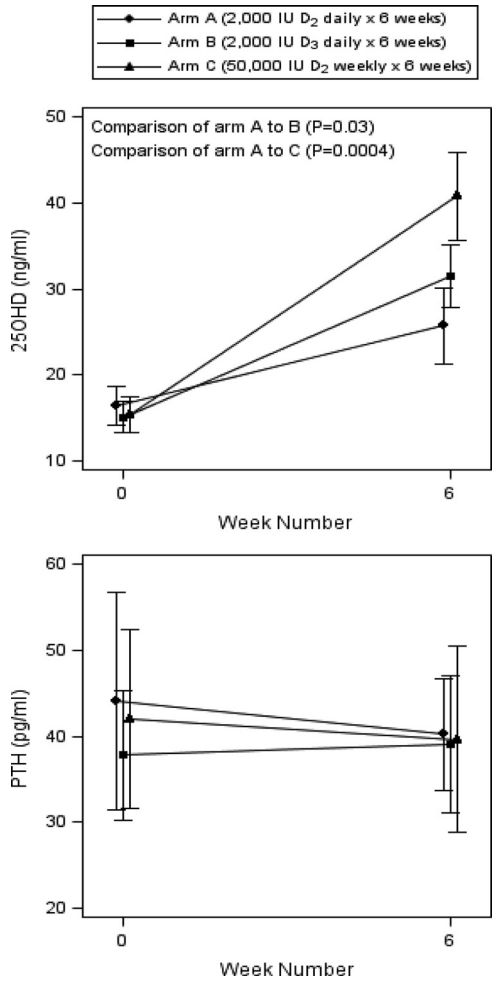


**FIG. 2.** 25OHD and PTH at wk 0 and wk 6 by treatment arm. Shown are the mean and 95% confidence interval. The increase in 25OHD from wk 0 to wk 6 is less in arm A compared with arm B ($P = 0.03$) and arm C ($P = 0.0004$). No statistically significant changes were observed for change in PTH.

serum 25OHD concentration above 32 ng/ml. Table 2 also shows the change in serum calcium and phosphorus concentration, as well as the frequency of hypercalciuria at follow-up. No change in serum PTH concentration was observed in any of the treatment arms. In a secondary analysis, we found that season at enrollment, follow-up, or crossing seasons was not a significant predictor of change in serum 25OHD concentration. IBD diagnosis (CD vs. UC) and adherence to therapy (100% *vs.* otherwise) were not significant predictors, even when adjusted for treatment arm. The seven subjects with serum 25OHD concentration ≤ 20 mg/ml at follow-up differed from the ones who achieved serum 25OHD concentration >20 ng/ml only in treatment assignment (five in arm A, one in arm B, and one in arm C; $P = 0.04$), weight [median (interquartile range, IQR), 66 (65–98) *vs.* 56 (48–68) kg; $P = 0.04$), and vitamin D dose/kilogram [median (IQR), 1296 (1275–1481) *vs.* 4602 (2147–5704) IU/kg; $P = 0.006$].

After modeling PTH response to 25OHD at baseline and follow-up, neither linear nor quadratic regression resulted in slopes statistically different from zero. Using a locally weighted least-squares regression, we found no threshold effect in the relationship between 25OHD and PTH. No participants experienced hypercalcemia, hyperphosphatemia, or serum 25OHD concentration higher than 68 ng/ml after treatment.

Table 3 shows the frequency of clinical adverse events, participant attrition, and study drug adherence. Adverse events occurred in one third of all participants, with the majority experiencing a single event, regardless of treatment assignment. Most commonly reported events were nausea (n = 6), increased thirst and loss of appetite (n = 5 each) and pruritus (n = 4), followed by drowsiness and increased urination frequency (n = 3 each); abdominal pain, bone pain, headache, and constipation (n = 2 each); rash, sensitive eyes, vomiting, irregular heartbeat, dry mouth, and muscle pain (n = 1 each). The occurrence of these events did not differ between arms. All adverse events were mild or moderate. One participant in arm B was withdrawn by the investigators due to an allergic reaction (rash on face and trunk) after 2 d of receiving study medication. Two participants in arm B were withdrawn after 2 wk of receiving the wrong study medication formulation, with no adverse event.

## Discussion

We found that 50,000 IU of oral vitamin $D_2$ weekly and 2,000 IU of oral vitamin $D_3$ daily for 6 wk were superior to 2,000 IU of oral vitamin $D_2$ daily for 6 wk in raising serum 25OHD concentration in children and adolescents with IBD and vitamin D insufficiency. Serum 25OHD concentration increased on average by 130% and 190% in arms B and C, respectively, compared with just 62% in arm A. Given the fact that 2,000 IU of daily vitamin $D_2$ for 6 wk left 25% of subjects untreated, we would not recommend using this regimen for treatment of vitamin D insufficiency in this population. We found that a cumulative dose of either 84,000 IU of vitamin $D_3$ (arm B) or 300,000 IU of vitamin $D_2$ (arm C) was successful in raising serum 25OHD concentration above 20 ng/ml in 95% of subjects. However, 62% of participants in arm B and 25% of participants in arm C did not achieve serum 25OHD concentration above 32 ng/ml. We estimate that a cumulative dose of 400,000 IU of vitamin $D_2$ or 220,000 IU of vitamin $D_3$ would be sufficient to achieve this level. We also found that all regimens were safe and well-tolerated. Change in serum PTH concentration did not differ between treatment arms.

**TABLE 3.** Clinical adverse events (AE), attrition, and compliance

| Characteristic | All | Treatment arms | | | *P* overall[a] |
|---|---|---|---|---|---|
| | | A | B | C | |
| Dose | | 2,000 IU $D_2$ daily | 2,000 IU $D_3$ daily | 50,000 IU $D_2$ weekly | |
| n | 71 | 24 | 24 | 23 | |
| AE | | | | | |
| Subjects with AE | 23 (32%) | 8 (33%) | 9 (38%) | 6 (26%) | 0.70 |
| AE per subject | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0 (0–1) | 0.64 |
| 0 | 48 (68%) | 16 (67%) | 15 (63%) | 17 (74%) | |
| 1 | 14 (20%) | 6 (25%) | 4 (17%) | 4 (17%) | |
| 2 | 6 (8%) | 1 (4%) | 4 (17%) | 1 (4%) | |
| 3 | 2 (3%) | 1 (4%) | 1 (4%) | 0 (0%) | |
| 9 | 1 (1%) | 0 (0%) | 0 (0%) | 1 (4%) | |
| Attrition | | | | | |
| Withdrawn; lost to follow-up | 10 (14%) | 4 (17%) | 3 (13%) | 3 (13%) | 1.00 |
| Withdrew consent | 1 | 0 | 0 | 1 | |
| Withdrawn by investigator | 3 | 0 | 3 | 0 | |
| Lost to follow-up | 6 | 4 | 0 | 2 | |
| Vitamin D compliance | | | | | |
| Subjects with compliance data | 56 (79%) | 18 (75%) | 20 (83%) | 18 (78%) | 0.78 |
| % of vitamin D study doses taken[b] | 100 (100–100) | 100 (100–100) | 100 (86–100) | 100 (100–100) | 0.21 |
| % fully compliant (among 56 with data)[b] | 44 (79%) | 14 (78%) | 14 (70%) | 16 (89%) | 0.43 |

Data are expressed as number (percentage), mean ± SD, or median (IQR).

[a] From Pearson $\chi^2$, Fisher exact test, ANOVA, or Kruskal-Wallis test, as appropriate for the distribution of the outcome.

[b] The analyses were based on subjects who had vitamin D compliance data.

Studies of the treatment of vitamin D insufficiency in older children and adolescents are almost nonexistent, with only one reporting successful vitamin D repletion using 50,000 IU weekly for 8 wk (21). A trial in healthy toddlers used vitamin D regimens identical to ours; the higher dose was as efficacious as the lower dose, without differences in adverse events (22). Studies in healthy adults showed that vitamin D replacement doses achieve predictable increases in serum 25OHD concentrations, which are inversely related to weight, BMI, and starting serum 25OHD concentration (23, 24). Principles behind these findings include the difference in distribution volume depending on weight, as well as differences in fat content, given the fact that vitamin D sequesters in fat tissue (25, 26). We found that the increment in serum 25OHD concentration was: 1) significantly greater in participants who received the higher dose; 2) lower than that achieved in healthy toddlers (22); and 3) inversely related to weight among participants who received high dose vitamin $D_2$ ($r = -0.44$; $P = 0.05$). We observed that participants who failed treatment were heavier. We conclude that a weight-adjusted vitamin D dose may be more appropriate and safe in children.

A dose of vitamin $D_3$ identical to a dose of vitamin $D_2$ increased serum 25OHD concentration 68% more than vitamin $D_2$ in our trial. This finding is in accordance with previous observations that vitamin $D_3$ is two to three times more "potent" than vitamin $D_2$ in terms of elevations in serum 25OHD concentration and longer duration of this result (12, 13). This difference is thought to be related to the higher affinity of vitamin $D_3$ to the vitamin D binding protein, which is the sole carrier of circulating vitamin D (27).

Pediatric populations with chronic diseases associated with impaired vitamin D bioavailability such as cystic fibrosis may require increased repletion and maintenance doses (28, 29). Existing studies of vitamin D absorption in patients with IBD have produced conflicting results (30, 31). Studies in healthy subjects calculated the slope of the rise in serum 25OHD concentration with supplementation (24, 32). Despite some methodological differences between these studies and ours, we found similar increases in serum 25OHD concentration per unit dose of vitamin D; we observed a rise of 0.8 to 1.1 ng/ml for every 10,000 IU of vitamin $D_2$ and 2 ng/ml for every 10,000 IU of vitamin $D_3$. These findings suggest that vitamin D absorption is not decreased in young patients with IBD compared with healthy subjects.

Although serum PTH concentration has been shown to have a small, inverse correlation with serum 25OHD concentration in both adults and children (33, 34), this was not apparent in our trial. Change in PTH was not different between arms. Interestingly, baseline PTH values were lower than reference PTH values for healthy children of similar age in our geographic area (2, 34), although our participants were vitamin D insufficient and had normal serum calcium and magnesium concentrations and calcium intake typical for age (35). Blunted PTH response and functional hypoparathyroidism have been described

among patients with burns (36) and in pediatric patients with systemic lupus erythematosus, another chronic inflammatory condition (37). Its pathogenesis has not been completely elucidated. Evidence exists that inflammatory cytokines (38) and antibodies against the calcium-sensing receptor (39, 40) directly up-regulate the expression of the calcium sensing receptor, driving downward the calcium level needed to stimulate PTH secretion. Systematic studies including healthy controls are needed to identify the prevalence of functional hypoparathyroidism in children with IBD and its pathogenesis.

All regimens examined were well-tolerated. A reported adverse event occurrence rate of 32% may be considered high, but it was similar in all arms. We may have overestimated the true adverse event rate because there may be overlap between adverse events reported and symptoms of IBD.

Another issue that deserves mention is that of adherence to treatment. Although this did not reach statistical significance, adherence was better with the weekly than the daily regimens. Given that our population consists of adolescents with a chronic illness that requires of them to take several daily medications, a weekly supplement may be a welcome and more viable option.

Our study is subject to limitations. First, it lacked a healthy control group, which led us to compare responses to treatment and other laboratory values only with literature controls. Although both vitamin $D_2$ and $D_3$ were provided in liquid form, vitamin $D_2$ has propylene glycol as an additive, whereas vitamin $D_3$ contains water, gum arabic emulsifier base, and sesame oil. Thus, the bioavailability of vitamin D may have been different between these two formulations.

In conclusion, we found that both 2,000 IU of daily vitamin $D_3$ and 50,000 IU of weekly vitamin $D_2$ were superior to 2,000 IU of daily vitamin $D_2$, all taken orally for 6 wk, in raising serum 25OHD concentration in young patients with IBD and vitamin D insufficiency. Whereas high-dose vitamin $D_2$ and vitamin $D_3$ were successful in treating insufficiency, the regimens were at best 75% successful (high vitamin $D_2$ dose) in achieving a 25OHD level >32 ng/ml. All regimens were well-tolerated. We did not observe changes in serum PTH concentrations with any of the regimens. Further studies are needed to define a specific target serum 25OHD concentration and the best regimen by which to achieve and maintain this in young patients with IBD. Moreover, studies are needed to examine the relationship between PTH and 25OHD in this population. Based on our findings, we would not recommend the use of 2,000 IU of daily oral vitamin $D_2$, for 6 wk, as treatment of vitamin D insufficiency in young patients with IBD.

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