



Pilot Study Evaluating Efficacy of 2 Regimens for Hypovitaminosis D Repletion in Pediatric Inflammatory Bowel Disease

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Tangpricha:

A PILOT STUDY EVALUATING EFFICACY OF TWO DOSING REGIMENS FOR REPLETION OF HYPOVITAMINOSIS D IN PEDIATRIC INFLAMMATORY BOWEL DISEASE

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Abstract

BACKGROUND/AIMS—Vitamin D is critical for skeletal health, hypovitaminosis D is common in pediatric IBD, yet optimal repletion therapy is not well studied. We aimed to conduct a pilot trial comparing the efficacy of two Vitamin D regimens of weekly dosing for repletion of hypovitaminosis D in pediatric IBD.

METHODS—Subjects identified from our IBD clinic with 25-hydroxyvitamin D (25(OH)D) concentrations below 30 ng/mL were randomized to 10,000 (n=18) or 5,000 (n=14) IU of oral vitamin D3/10 kg body weight/week for six weeks. Serum 25(OH)D, Ca, and PTH concentrations were measured at baseline, week 8 and week 12.

RESULTS—In the higher dosing group, serum 25(OH)D increased from 23.7 ±8.5 ng/mL at baseline to 49.2 ±13.6 ng/mL at 8 weeks; P<0.001. In the lower dosing group, serum 25(OH)D increased from 24.0 ±7.0 ng/mL at baseline to 41.5 ±9.6 ng/mL at 8 weeks; P<0.001. At 12 weeks, serum 25(OH)D concentrations were 35.1 ± 8.4 ng/mL and 30.8 ± 4.2 ng/mL for the higher and lower dose regimens, respectively. Mean serum Ca and PTH concentrations did not significantly change during the study. No patient exhibited hypercalcemia, and no serious adverse events occurred.

CONCLUSIONS—Both treatment arms were safe and effective at normalizing vitamin D nutriture in pediatric IBD. While significant repletion of 25(OH)D concentration was achieved in the lower dose group at 8 weeks, this effect was lost by the 12-week follow-up. Maintenance

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vitamin D therapy following initial repletion is likely required to maintain long-term normalized vitamin D status.

Keywords

vitamin D; Crohn's disease; ulcerative colitis; children

BACKGROUND & AIMS

The inflammatory bowel diseases (IBD) Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, inflammatory diseases of the digestive tract that have significant impact on growth and development in children and on overall health, nutritional deficiencies and quality of life across all age groups [1]. The natural history of these diseases can range from mild symptoms, that may be relatively well controlled with medical management, to severe, recalcitrant disease with numerous complications requiring multiple intestinal resection surgeries to excise inflamed bowel.

Vitamin D has been comprehensively studied for its effects in calcium, phosphorus and bone metabolism. However, several lines of evidence suggest that vitamin D plays an important role in immune regulation, innate immune responses, adaptive immunity and immune tolerance [2]. Vitamin D deficiency is common in patients with IBD, as indicated by numerous retrospective and cross sectional studies [3–5]. In addition, severe compromised bone health in IBD can occur and result in osteoporosis and increased fracture risk [6]. There is growing epidemiological evidence to suggest that vitamin D plays a role in the development of IBD and influences disease severity [3]. While the animal and in-vitro models showing the vital role of vitamin D in moderating disease activity and immune tolerance in IBD, the evidence from human IBD studies are still developing [2].

Serum 25-hydroxyvitamin D (25(OH)D) is the marker of vitamin D status in humans but there has been speculation of what defines an adequate level of 25(OH)D in humans. The American Academy of Pediatrics (AAP) and the Institute of Medicine (IOM) has defined 20 ng/mL or greater as a sufficient serum 25(OH)D concentration [7, 8]. The Institute of Medicine specifically argues that levels above 30 ng/mL do not provide additional benefit. However, many adult studies do suggest a higher cutoff of 32 ng/mL as the norm, and this has increasingly become the accepted norm in studies [9–12].

Known risk factors for vitamin D insufficiency or deficiency in IBD include seasonality, severe disease activity, extensive small bowel involvement or resection, dark skin pigmentation, and corticosteroid treatment [13]. Joint guidelines from the North American and European Societies for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN and ESPGHAN, respectively) [5], published in 2011, recommend that pediatric gastroenterologists treating pediatric IBD patients consider monitoring vitamin D status yearly and that they treat hypovitaminosis D to establish and maintain optimal vitamin D levels. These recommendations suggest the use of a weekly vitamin D treatment regimen, as issues of compliance in pediatric and adolescent patients with chronic diseases are of significant concern. Furthermore, several studies have suggested that vitamin D₃ (cholecalciferol) has 2 to 3 fold greater bioavailability over vitamin D₂ (ergocalciferol),

which is commonly prescribed as a high dose weekly treatment regimen for vitamin D deficiency in the United States [14–17].

Focused studies of vitamin D dosing in children with inflammatory bowel disease had been virtually absent from the literature until 2011. Recent pioneering studies by Pappa et al. [18, 19] have begun to explore potential dosing regimens for the treatment of hypovitaminosis D in these children with IBD. The results from those studies suggest that higher weight-adjusted dosing may be more appropriate and safer in children. There is a need for higher and effective dosing regimen studies for repletion of vitamin D for hypovitaminosis in children with IBD.

The primary aim of this study was to compare the efficacy of two weekly oral dosing regimens of vitamin D₃ for the repletion of hypovitaminosis D in children and adolescents with known IBD. Secondary aims included (1) evaluation of the safety of high dose weekly dosing of vitamin D₃ in pediatric IBD patients and (2) evaluation of any differences in serum 25(OH)D levels among subjects as a function of skin pigmentation. Weekly regimens were chosen to improve compliance, which is a common concern with children and adolescents with IBD.

METHODS

Participants

Potential subjects were identified from the Pediatric IBD Clinics at Emory Children's Center & Children's Healthcare of Atlanta who had recently (within three months of enrollment) been screened for serum 25(OH)D concentrations as part of their routine care. Inclusion criteria mandated screening serum 25(OH)D level <30 ng/mL, age between 8–21 years, weight > 20 kg, and confirmed diagnosis of IBD (either CD or UC) by a pediatric gastroenterologist. Any patients with the inability to swallow the study drug capsules were also excluded. Since vitamin D metabolism can also be impacted by underlying chronic kidney or liver diseases, those with a known history of renal or hepatobiliary disease were excluded. We also did not include those who had a history of recent use of systemic corticosteroids (within 60 days of enrollment). Fitzpatrick skin pigmentation score and type [20], which are commonly utilized objective measures of skin pigmentation, were recorded for comparison in all subjects at enrollment. Subjects were randomized by permuted block design to one of two study arms by the Children's Healthcare of Atlanta Research Pharmacy. Both subjects and investigators were blinded to the group assignment. The research pharmacist also purchased the Vitamin D₃, packaged it, and dispensed it. The full trial protocol can be accessed, on request from the authors.

Vitamin D Dosing

Vitamin D₃ was purchased from a commercial source (Nature's Bounty, Inc., Bohemia, New York). Subjects were given either 5,000 IU vitamin D₃ per 10 kg body weight once weekly for a total of 6 weeks (maximum weekly dose of 25,000 IU, maximum cumulative dose of 150,000 IU) or 10,000 IU vitamin D₃ per 10 kg body weight once weekly for a total of 6 weeks (maximum weekly dose of 50,000 IU, maximum cumulative dose of 300,000 IU).

Subjects and caregivers were contacted weekly by telephone throughout the intervention period of 6 weeks to ensure and document compliance with the study intervention. Pill count was done at follow up visits.

Sample collection and laboratory assays

Whole blood was collected from all subjects at the time of enrollment (baseline) and at 8 and 12 weeks (approximately 2 and 6 weeks, respectively, following the last dose of the study drug). Serum was isolated and stored at -80°C . Samples were analyzed in-batch for baseline and follow-up concentrations of serum 25(OH)D, total serum calcium (Ca), and parathyroid hormone (PTH). Serum 25(OH)D concentration was analyzed in one single batch by liquid chromatography-tandem mass spectrometry (LC/MS/MS). Ca concentrations in serum were determined using colorimetric assays purchased from Point Scientific, Inc., Canton, MI 48188. Serum PTH was determined using the FDA approved DiaSorin intact PTH immunoradiometric assay (IRMA). All three biochemical metrics were analyzed in-batch by Heartland Assays, Ames, IA.

Sample size

This trial was designed to compare the efficacy of two treatment arms to replete hypovitaminosis D. Given 20 patients per group ($N = 40$ total) we had greater than 90% power to detect a 10 ng/mL mean increase in serum 25(OH)D levels from baseline to week 8 in each dosing group. Power was calculated assuming a standard deviation of differences of 10 ng/mL using a paired t-test with a 0.05 level of significance. In addition, using similar assumptions, 20 patients per group achieves 80% power to detect an average difference of 9.1 ng/mL between dosing groups at 8 weeks using a two-sample t-test.

Safety and clinical adverse events

Safety was based on evaluation of serum calcium and PTH levels at baseline, week 8 and week 12. Patients were also screened at each study visit and each weekly phone call for clinical signs or symptoms of hypercalcemia with either intervention during the study period. Specifically, patients were asked regarding gastrointestinal symptoms (cramps, pain, diarrhea, vomit, nausea) and musculoskeletal symptoms (pain, cramps, twitches). Clinical adverse events were reported at each visit using specifically designed case report forms (CRFs). All participants reporting adverse events were retained for analysis regardless of withdrawn status.

Statistical Methods

Statistical analyses were performed using SAS 9.3 (Cary, NC). Statistical significance was assessed at the 0.05 level unless otherwise noted. Analysis was done using intention to treat design and randomization assignments were maintained. Two-sample t-tests, Mann-Whitney U tests, and Chi-square tests were used to compare demographic and clinical characteristics between randomization groups. Repeated measures analysis of variance models were used to examine serum 25(OH)D concentrations within and between dosing groups over time while controlling for the correlation among observations made on the same study participant. For these models an auto-regressive correlation structure was used. Within each dosing group,

serum 25(OH)D concentrations were compared at different time points (i.e., week 0, week 8 and week 12) using a Tukey-Kramer multiple comparison procedure. Interactions between dosing group and time were initially included in all models and retained if $p < 0.10$. Similar analyses were used to compare Ca and PTH concentrations over time and between groups.

Ethical Considerations and Institutional Oversight

This interventional clinical study was conducted in accordance with the principles of the Declaration of Helsinki and with appropriate approval and oversight by the Institutional Review Boards of Emory University and Children's Healthcare of Atlanta.

Access to Study Data

All authors had access to the study data and have reviewed and approved this final manuscript.

RESULTS

Treatment Assignment

The subject enrollment flow diagram of the pilot study is given as figure 1. We enrolled a total of 34 patients to our study between April 8 and November 25, 2013. Sixteen subjects were randomized to the 5,000 IU/10 kg group, and 18 subjects were randomized to the 10,000 IU/10kg group. Two subjects withdrew from the study after enrollment; one of these subjects withdrew after a single episode of vomiting that occurred in the week after starting the intervention, and the other subject withdrew due to prolonged diarrhea, which was preexisting at enrollment. Twenty-two subjects completed all three study visits, five subjects completed only two study visits, and five subjects completed only the enrollment visit and did not return for follow-up thereafter. Randomization was balanced across both study groups (see Table 1).

Demographics

Our study cohort had a mean age of 16 years ($SD \pm 2.8$), range 11–20y. Study participants were predominantly males (63%) and AA (66%). The vast majority of patients had CD (88%) and had darker skin types groups using the Fitzpatrick scales. There were no significant differences in demographic characteristics between randomization groups of Vit D 5,000 IU/10 kg and 10,000 IU/10kg (Table 1).

Vitamin D Concentrations

Baseline serum 25(OH)D concentrations were evenly matched between the 5,000/10kg and 10,000 IU/10kg groups at baseline (week 0; 24.0 ± 7.0 ng/mL and 23.7 ± 8.5 ng/mL, respectively; $P=0.920$). A significant increase in serum 25(OH)D concentrations occurred in both treatment groups at week 8, with the higher dosing group being superior (increase of mean 25(OH)D from 23.7 ± 8.5 ng/mL at baseline to 49.2 ± 13.6 ng/mL at 8 weeks; $P<0.001$) to the lower dosing group (increase of mean 25(OH)D from 24.0 ± 7.0 mg/mL at baseline to 41.5 ± 9.6 ng/mL at 8 weeks; $P<0.001$) (Table 2 & Figure 2). While not statistically different, the mean 25(OH)D concentration for the 10,000 IU/10 kg dosing

regimen was higher than for the 5,000 IU/10kg regimen at both 8 and 12 week follow-up visits (49.2 ± 13.6 and 41.5 ± 9.6 at week 8; $P=0.105$, versus 35.1 ± 8.4 and 30.8 ± 4.2 at week 12; $P=0.122$, respectively) We also looked at patients under 50 kg. We had a total of 11 subjects (34%) less than 50kg, 7 of them were between 45–49 kg and 4 were below 45 kg. The serum 25(OH)D concentration of the patients below 50kg at baseline, week 8 and week 12 had a similar trend to the entire group of patients (10,000 IU/kg group had a mean 24(OH)D serum of 27.0 ± 4.3 ng/ml at baseline, 50.8 ± 11.5 ng/ml at week 8, and 36.1 ± 6.4 ng/ml at week 12; 5,000 IU/kg group had a mean 24(OH)D serum of 21.3 ± 8.0 ng/ml at baseline, 41.0 ± 12.0 ng/ml at week 8, and 30.7 ± 6.2 ng/ml at week 12.)

Calcium & PTH

For the 10,000 IU/10kg regimen there was no significant change in mean serum Ca concentration throughout the study period. There was a small increase in serum Ca for the 5,000 IU/10kg group between baseline and week 8 (11.3 ± 0.7 to 11.9 ± 0.7); however, after adjusting for multiple comparisons, this difference was not statistically significant. Similarly, for the 5,000 IU regimen there was no significant change in the mean serum PTH concentrations throughout the study period. For the 10,000 IU regimen there was a decrease in PTH from baseline to week 8 (45.8 ± 23.7 to 33.6 ± 14.8); however after adjusting for multiple comparisons, this difference was not statistically significant. Furthermore, serum Ca and PTH concentrations were similar between groups at each study period (Table 3). Mean serum Ca concentrations (mg/dL) for the 5,000 IU/10 kg group and 10,000 IU/10 kg group were 11.3 ± 0.7 versus 11.4 ± 0.5 ($P=0.644$) at week 0, 11.9 ± 0.7 versus 11.7 ± 0.7 ($P=0.573$) at week 8, and 11.4 ± 0.8 versus 11.7 ± 0.7 ($P=0.573$) at week 12, respectively. Mean serum PTH concentrations (pg/mL) for the 5,000 IU/10 kg group and 10,000 IU/10 kg group were 37.2 ± 20.1 versus 45.8 ± 23.7 ($P=0.289$) at week 0, 30.2 ± 13.3 versus 33.6 ± 14.8 ($P=0.647$) at week 8, and 27.3 ± 9.5 versus 38.9 ± 17.4 ($P=0.061$) at week 12, respectively.

Safety

No subject exhibited clinical signs or symptoms of hypercalcemia with either intervention during the study period, and no serious adverse events were observed. Furthermore, all serum Ca and PTH values did not significantly increase from baseline through the intervention period.

DISCUSSION

This pilot trial provides new information to inform optimization of vitamin D₃ (cholecalciferol) repletion dosing for hypovitaminosis D in pediatric IBD patients. Current guidelines for treatment of vitamin D insufficiency in healthy children have included wide dosing ranges (84,000 to 600,000 IU, cumulatively), without specific guidance on weight- or age-based dosing of vitamin D [8]. It has been suggested that higher doses are necessary in children and adolescents with IBD for a variety of reasons [4], and cumulative doses of 220,000 IU vitamin D₃, independent of age or weight, have been estimated to provide sufficient repletion of hypovitaminosis D in pediatric IBD patients [19]. Our results show significant elevations in serum 25(OH)D concentrations above 30 ng/mL with both 5,000 IU

vitamin D₃/10 kg once weekly for a total of 6 weeks (maximum weekly dose of 25,000 IU, maximum cumulative dose of 150,000 IU) or 10,000 IU vitamin D₃/10 kg once weekly for a total of 6 weeks (maximum weekly dose of 50,000 IU, maximum cumulative dose of 300,000 IU). This was notable both at 8 and 12 week follow-up visits indicating both dosing regimens are effective in replenishing vitamin D in hypovitaminosis D in pediatric IBD. A novel component of our trial was that we used much higher treatment doses of vitamin D₃ as compared to other pediatric trials [18, 19] which used a maximum daily dose of vitamin D₃ 2000 IU with higher weekly dosing of vitamin D₂ not D₃ [19]. Another key finding from our study is our demonstration that serum 25 (OH)D concentrations in both patient groups began to decrease once treatment was stopped suggesting the need for longer duration of repletion and/or maintenance therapy.

An important area of investigation has been differences in vitamin D status with regards to ethnicity/race. Our group has previously demonstrated that African-Americans tend to have low vitamin D status or vitamin D deficiency regardless of their IBD disease status [25]. Overall bone health appears to be impacted by IBD and vitamin D status in Caucasians, whereas African-Americans' bone health may not be affected by the presence of IBD or by African-Americans' overall vitamin D status. In our current study, we used an objective method of classifying skin color pioneered by Fitzpatrick [20]. Stratifying by skin pigmentation, we did not see differences in baseline or after treatment vitamin D status, but these data are limited by our small sample size.

It is also important to note that our study utilized vitamin D₃ (cholecalciferol), which has greater bioavailability than vitamin D₂ (ergocalciferol), and we have demonstrated that a higher dosing regimen of vitamin D₃ has a well-tolerated safety profile in terms of serum calcium and PTH levels. Furthermore, given that we did not additionally give our patients supplemental calcium, our results suggest that improved vitamin D status improves calcium economy in patients with IBD removing the need for prescribing additional calcium as has been done in previous trials by Pappas et al. While serum PTH concentration has been shown in both adults and children to have a small, inverse correlation with serum 25OHD concentration [27, 28], in our study there was no statistically significant change in mean serum Ca or PTH concentrations throughout the study for either treatment group, and no differences were observed between treatment groups.

Our study was limited by our small sample size. The study was powered to detect differences between vitamin D dosing regimens at 8 weeks given 20 patients per group. Our effective sample size for analysis was only 32 (14 and 18 for 5,000 and 10,000 respectively) due to patients leaving the study prematurely and unintentional corticosteroid exposure. Thus, we were inadequately powered to detect smaller differences in our outcomes measures between dosing groups. However, we were able to demonstrate that these high vitamin D dosing regimens were safely able to increase serum 25(OH)D levels and effectively replete hypovitaminosis D in our study cohort. In addition, while not statistically significant, the 10,000 IU/10kg regimen resulted in mean serum 25(OH)D levels that were 19% higher than the 5,000 IU/10kg regimen group at 8 weeks. The lack of a control group did not allow us to compare our findings against healthy children and adolescents.

Another limitation was the lack of diet history and lack of sun exposure history which certainly affects a patient's serum 25(OH)D level. We did not collect this data because this data is frequently prone to recall bias.

Finally, our cohort consisted of older adolescents (mean age 16 ± 2.8 y) who are predominantly males (59%). Thus our results may not be generalizable to a younger female demographic. Also, our mean 25(OH)D level at the start of the study was 24.0 ng/mL. As we had mentioned earlier, there is a large variation in the literature of what constitutes a deficiency [7, 8]. For our study we chose to define serum 25(OH)D levels ≤ 20 ng/mL as deficient, and serum levels >20 but ≤ 30 ng/mL as suboptimal as has been suggested by several studies [9–12]. Due to the initial serum 25(OH)D levels being in the suboptimal category, our results may not be generalizable to lower serum levels.

Despite the small sample size, this is the first randomized pediatric trial that demonstrated effective repletion of hypovitaminosis D using high dose vitamin D₃ supplementation in IBD patients. This study provides initial evidence to be further corroborated with larger scale trials - that vitamin D₃ doses as high as 10,000 IU per 10 kg weekly are safe and well-tolerated.

In conclusion, we have found that either 5,000 or 10,000 IU per 10 kg weekly dosing with oral vitamin D₃ for six weeks is both safe and effective at normalizing vitamin D nutrition in pediatric IBD patients. Based on 25(OH)D concentrations measured at 12 weeks, our data also suggests that the effect of weekly dosing is diminished 12 weeks out. This suggests that perhaps after an initial induction regimen, repletion needs to continue for a longer maintenance duration to potentially have a more sustained effect on vitamin D nutrition. Therefore, we recommend both repletion and maintenance vitamin D therapy is necessary to replete and maintain optimal vitamin D status, and further clinical studies are merited to establish optimal chronic vitamin D₃ dosing regimens in pediatric IBD.

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Abbreviations

| | |
|----------------|----------------------------|
| 25(OH)D | 25-hydroxyvitamin D |
| AA | African American |
| Ca | Calcium |
| CD | Crohn's Disease |
| IBD | Inflammatory Bowel Disease |
| IU | International Units |
| Kg | kilograms |
| PTH | Parathyroid Hormone |

UC Ulcerative Colitis

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SUMMARY BOX**What is known about this subject?**

- Hypovitaminosis D is a well-known comorbidity in inflammatory bowel disease, and its implications in skeletal health and immune function are the subject of an ever-expanding body of literature.
- Vitamin D dosing recommendations for this group are limited by a relative lack of clinical research to inform such decisions, especially with regards to pediatric inflammatory bowel disease.

What are the new findings and/or what is the impact on clinical practice?

- We performed a randomized pilot comparing efficacy and safety of two weight-based dosing regimens using oral vitamin D3 given once weekly for six weeks.
- Our study builds on the very broad vitamin D dosing recommendations from the Institute of Medicine and American Academy of Pediatrics as well as the more relevant, recent pioneering work of Pappa et al.
- Our study demonstrates significant repletion of hypovitaminosis D in pediatric inflammatory bowel disease patients without compromising safety, and offers a practical approach to vitamin D repletion therapy in the clinical setting using higher dosing of oral vitamin D3.

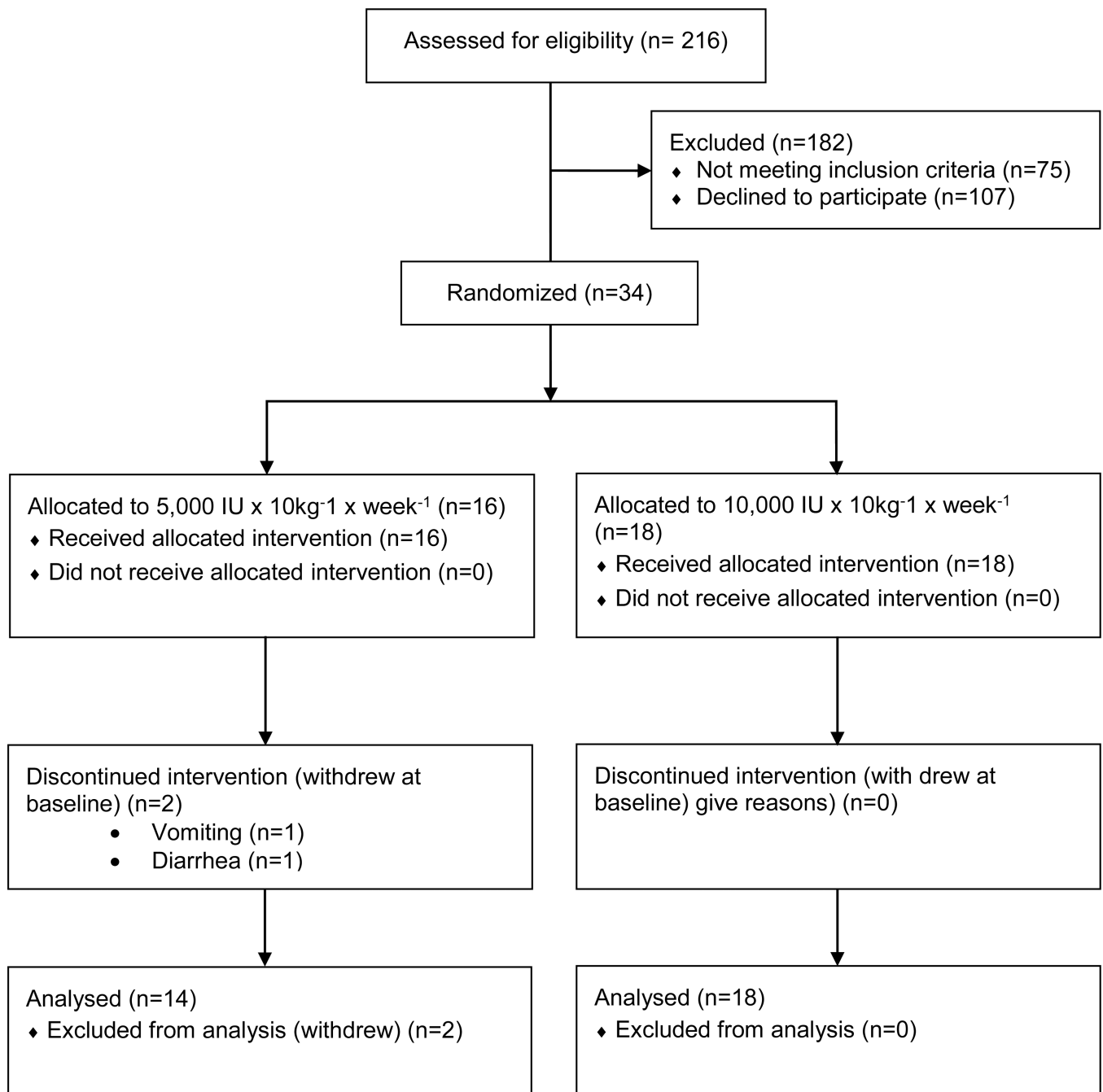


Figure 1.
Subject recruitment flow diagram showing selection and final disposition of study participants.

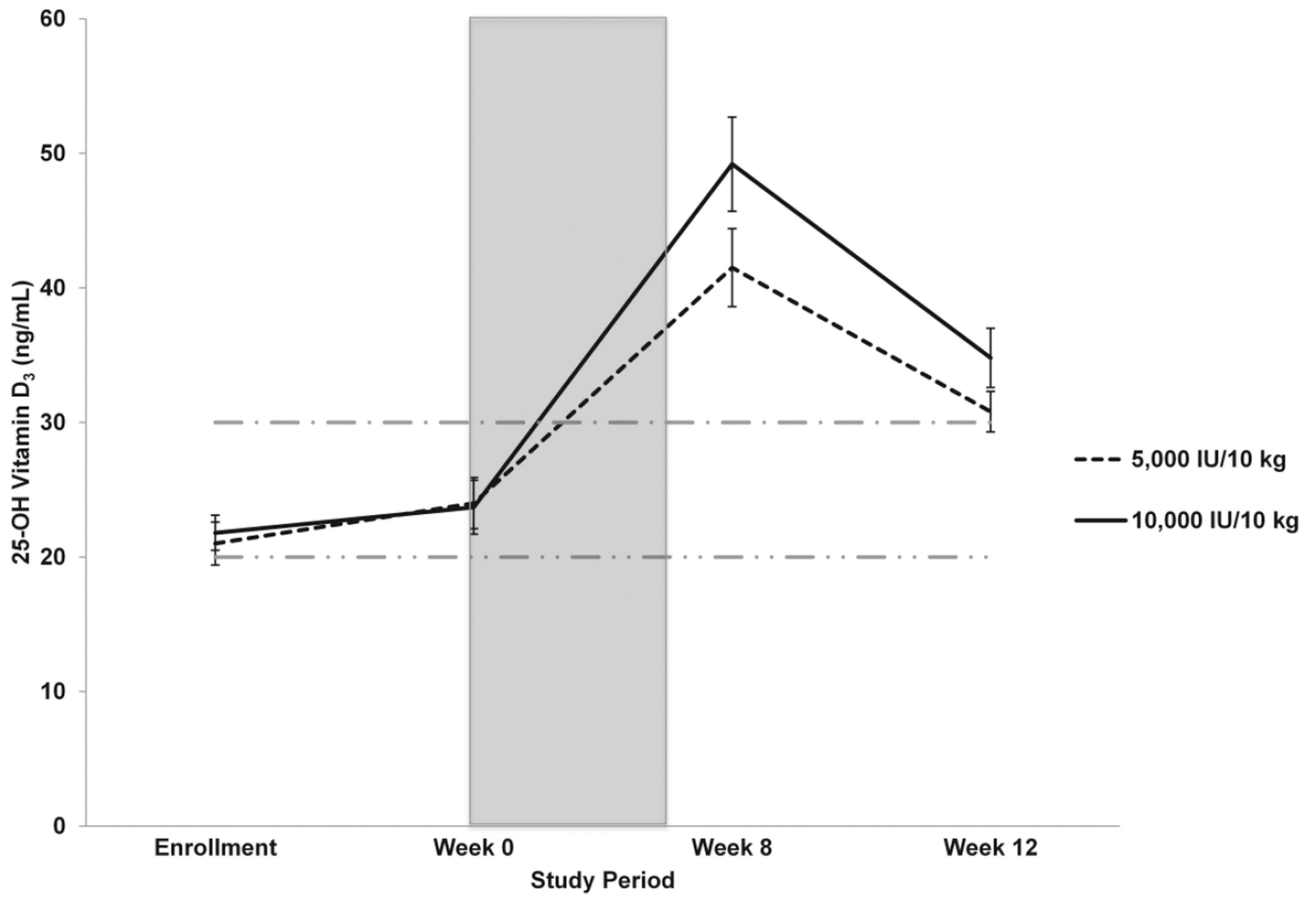


Figure 2. Mean 25-OH vitamin D₃ concentrations enrollment, at treatment start (week 0), 8 weeks and 12 weeks following the start of treatment. Standard error bars are shown. The gray box indicates the timing of the intervention (oral cholecalciferol once weekly for a total of 6 doses).

Table 1

Comparison of Demographic and Clinical Variables Between Groups.

| Characteristic | | Vitamin D ₃ Treatment Group | | P-value |
|--------------------------------|--------|--|----------------------------|---------|
| | | 5,000 IU/10kg (n = 14) | 10,000 IU/10kg (n = 18) | |
| Age (years) | | | | |
| Mean ± SD | -- | 15.8 ± 3.2 | 15.6 ± 2.5 | 0.812 |
| Weight (kg) | | | | |
| Mean ± SD | | 53.3 ± 13.6 | 58.1 ± 22.8 | 0.463 |
| Sex | Female | 5 (35.7%) | 7 (38.9%) | 0.854 |
| | Male | 9 (64.3%) | 11 (61.1%) | |
| Race | White | 3 (21.4%) | 5 (27.8%) | 0.869 |
| | AA | 10 (71.4%) | 11 (61.1%) | |
| | Other | 1 (7.1%) | 2 (11.1%) | |
| Diagnosis | CD | 11 (78.6%) | 17 (94.4%) | 0.295 |
| | UC | 3 (21.4%) | 1 (5.6%) | |
| [‡] Skin Type | | | | |
| Skin Type I–II | | 3 (23.1%) | 2 (11.1%) | 0.418 |
| Skin Type III–IV | | 2 (15.4%) | 6 (33.3%) | |
| Skin Type V–VI | | 8 (61.5%) | 10 (55.6%) | |
| [‡] Skin Score | | | | |
| Mean ± SD | -- | 26.1 ± 13.6 | 29.2 ± 7.9 | 0.469 |

AA – African American; CD – Crohn’s disease; SD – standard deviation; UC – ulcerative colitis.

[‡]The Fitzpatrick Scale is as follows: Type I (scores 0–6) pale white; blond or red hair; blue eyes; freckles — always burns, never tans. Type II (scores 7–13) white; fair; blond or red hair; blue, green or hazel eyes — usually burns, tans minimally. Type III (scores 14–20) cream white; fair with any hair or eye color; quite common — sometimes mild burn, tans uniformly. Type IV (scores 21–27) moderate brown; typical Mediterranean skin tone — rarely burns, always tans well. Type V (scores 28–34) dark brown; Middle Eastern skin types — very rarely burns, tans very easily. Type VI (scores 35+) deeply pigmented dark brown to black — never burns, tans very easily. Mean skin type expressed as an Arabic numeral equivalent to the Roman numeral Fitzpatrick skin type scale I through VI and mean scores are reported.

Table 2

Comparison of serum 25-OH vitamin D concentrations at weeks 0, 8, and 12. P-values reflect pairwise comparison of 25(OH)D concentrations between study visits. Significant p-values are in bold, these are for within group comparisons at week 0,8 and 12.

| Vitamin D ₃ Treatment Group | Mean [25(OH)D ₃] ± SD (ng/mL) | | | p-Value |
|---|---|-------------|------------|--|
| | Week 0 | Week 8 | Week 12 | |
| 5,000 IU/10 kg/wk | 24.0 ± 7.0 | 41.5 ± 9.6 | 30.8 ± 4.2 | P<0.001 (wk 0 vs wk 8) P=0.132 (wk 0 vs wk 12) P<0.001 (wk 8 vs wk 12) |
| 10,000 IU/10 kg/wk | 23.7 ± 8.5 | 49.2 ± 13.6 | 35.1 ± 8.4 | P<0.001 (wk 0 vs wk 8) P<0.001 (wk 0 vs wk 12) P<0.001 (wk 8 vs wk 12) |

Table 3

| Characteristic | Vitamin D group | | P* |
|---------------------------|--|---|-------|
| | 5,000 IU × 10 kg ⁻¹ , wk ⁻¹ | 10,000 IU × 10 kg ⁻¹ , wk ⁻¹ | |
| Week 0 | | | |
| Mean calcium (mg/dL) ± SD | 11.3±0.7 | 11.4±0.5 | 0.644 |
| Mean PTH (pg/mL) ± SD | 37.2±20.1 | 45.8±23.7 | 0.289 |
| Week 8 | | | |
| Mean calcium (mg/dL) ± SD | 11.9±0.7 | 11.7±0.7 | 0.573 |
| Mean PTH (pg/mL) ± SD | 30.2±13.3 | 33.6±14.8 | 0.647 |
| Week 12 | | | |
| Mean calcium (mg/dL) ± SD | 11.5±0.8 | 11.7±0.7 | 0.223 |
| Mean PTH (pg/mL) ± SD | 27.3±9.5 | 38.9±17.4 | 0.061 |

PTH-parathyroid hormone.

* P values are for the null hypothesis that there is no difference in mean calcium and PTH levels in the 5,000 and 10,000 IU × 10 kg⁻¹, wk⁻¹ at times week 0, 8 and 12.