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SAFETY AND EFFICACY OF HIGH DOSE DAILY VITAMIN D_3 SUPPLEMENTATION IN CHILDREN AND YOUNG ADULTS WITH SICKLE CELL DISEASE

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Abstract

Suboptimal vitamin D (vitD) status (<32 ng/ml) is ubiquitous among African American children with type SS sickle cell disease (SCD-SS). The vitD supplemental dose to normalize vitD status is unknown. Five to 20-year-old African-American children with (n=21) and without (n=23) SCD-SS were randomized to vitD_3 supplementation (4,000 or 7,000 IU/day) and evaluated at 6- and 12-weeks for changes in vitD and SCD status. A dose was considered unsafe if serum calcium was elevated associated with elevated serum 25 hydroxyvitamin D (25(OH)D)). At baseline 95% of subjects with SCD-SS and 87% of healthy controls had suboptimal vitD status (mean ± SD, 19.2 ± 7.2 and 22.3 ± 9.3 ng/ml, respectively). After 12-weeks supplementation, both D_3 doses were safe and well tolerated. Neither group achieved the a priori efficacy criterion of 25(OH)D ≥ 32 ng/ml in >80% of subjects (45% in SCD-SS and 63% in controls). However for both subjects with SCD-SS and healthy subjects by 12-weeks, deficient (< 20 ng/ml) vitD status was eliminated only in those receiving 7,000 IU/d. For subjects with SCD-SS, by 12-weeks there was a significant (all P<0.05) increase in fetal hemoglobin, decrease in HS-CRP, and reduction in the percentage of subjects with a high platelet count.

Keywords

Vitamin D; Sickle Cell Disease; Pediatrics; Supplementation

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INTRODUCTION

Sickle Cell Disease (SCD) is a hereditary disorder affecting primarily Africans and African Americans characterized by chronic hemolytic anemia and vaso-occlusive complications caused by sickle-shaped cells. Those homozygous for the SS allele (SCD-SS) are the most severely affected. Common clinical features of children with SCD-SS include poor growth and reduced lean body mass[1], poor dietary intake[2], deficits in bone mineral architecture[3] and reduced muscle strength and power[4]. Possible modifiable factors to ameliorate these health outcomes include correcting nutritional deficiencies; however few supplementation studies have been conducted in this population.

The pleiotropic effects of vitamin D (vit D) extend beyond the well-recognized role in bone health to include immunomodulatory, anti-inflammatory and regulation of skeletal muscle morphology and function[5,6]. Poor vit D status is ubiquitous among African American children with SCD-SS, with >90% of subjects with a 25 hydroxyvitamin D (25(OH)D) concentration <30 ng/ml[7]. Risk factors for poor vit D status include low vit D intake, skin pigmentation, inadequate sunlight exposure or unknown SCD associated factors. Despite encouraging observational and animal data[8], the potential role of daily vit D supplementation in the treatment of SCD has not been tested. However prior to full scale trials, the supplemental dose that optimizes vit D status in SCD need to be determined.

The purpose of this study was to assess the safety and efficacy of two oral daily doses (4,000 vs. 7,000 IU) of cholecalciferol (vit D_3) over a 12-week period in children and young adults with SCD and healthy controls. Safety was determined by serum calcium and 25(OH)D concentrations and efficacy by attaining 25(OH)D ≥32 ng/ml. We hypothesized that 1) both vit D_3 doses were safe with <5% incidence of elevated calcium (age and sex specific range) associated with elevated 25(OH)D (>160 ng/ml); and 2) daily vit D_3 supplementation for 12-weeks would result in the study defined target of 25(OH)D ≥32 ng/ml in >80% of subjects in both dose groups.

MATERIALS AND METHODS

Subjects

Participants for this study were 5- to 20-year-old African-American children with (n=22) and without SCD-SS (n=22). Children with SCD-SS were recruited from the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia (CHOP). Healthy subjects were recruited from the CHOP network of primary care centers and the greater Philadelphia region. Exclusion criteria for both groups included participation in another study impacting 25(OH)D, pregnant or lactating females, other chronic conditions or use of medications affecting growth, dietary intake, or nutritional status, use of vit D supplementation to treat vit D deficiency, and baseline elevated serum calcium concentration. Subjects taking supplements containing vit D (not part of prescribed treatment plan) were not eligible. Those willing to discontinue supplementation with approval of their medical provider were eligible after a two month washout period. Additional exclusion criterion for subjects with SCD were chronic transfusion therapy and for healthy subjects were body mass index (BMI) >85th percentile for age and sex[9]. The

first subject enrolled April 2012 and last subject was completed on January 2013 with visits at baseline, 6- and 12-weeks.

For this study, vit D status (25(OH)D concentration) was defined based upon the literature at the time of the onset of the study[10,11]: sufficient, ≥32 ng/ml; insufficient, <32 to 20 ng/ml; and deficient, <20 ng/ml. Intestinal calcium absorption efficiency has been shown to be positively associated with 25(OH)D until a threshold of 30 ng/ml[12] and regulation of intestinal calcium absorption is considered optimal at 25(OH)D >32 ng/ml[13]. This study used these published data to define the relationships between calcium and 25(OH)D. A 25(OH)D of 200 ng/ml has been considered the lower bound for potential toxicity above which risk for elevated calcium increases[14,15]. For this study, a vit D_3 dose was considered unsafe if it resulted in elevated 25(OH)D >160 ng/ml coupled with an elevated calcium (age and sex specific range). Current evidence suggests, compared to people with 25(OH)D <30 ng/ml, those with higher concentrations have reduced risk for many non-bone related health outcomes including immunomodulatory effects, potentially less cancer and overall mortality[15,16]. However, the ideal level to minimize the risk of these non-bone-related outcomes is not known. Thus, subjects with optimal and suboptimal vit D status were enrolled in this study.

This protocol was approved by Institutional Review Board at CHOP. Written informed consent was obtained from subjects ages 18 to 20 years and parents / legal guardians of subjects <18.0 years. Verbal assent was obtained from subjects 6 to <18 years. Safety was monitored weekly by study team and quarterly by an Independent Monitoring Committee.

Randomization and masking

Within each group (i.e. SCD and control), subjects were randomized to 4,000 (Vitacost Vitamin D_3, Boca Raton, FL) or 7,000 (Life Extension Vitamin D_3, Ft. Lauderdale, FL) IU vit D_3/day for 12 weeks using a double blind design. The two doses, provided as capsules, were identical in size, shape and color. Those unable to swallow capsules took 0.28 mL or 0.49 mL of 400 IU/d vit D_3 drops (Carlson D Drops, J.R. Carlson Laboratories, Inc. Arlington Heights, IL) in the 4,000 or 7,000 IU/d group, respectively. Doses were independently verified before and at the conclusion of the study (Tampa Bay Analytical Research, Inc., Largo, FL). Subjects were enrolled in the Spring (April–May), Summer (June–August) and Fall/Winter (September–January).

Anthropometry, pubertal status, dietary intake and questionnaires

Anthropometric measurements at each visit were obtained in triplicate according to standardized techniques[17] and the mean used for analysis. BMI was calculated (kg/m^2) from weight using a digital scale (Scaletronix, White Plains, NY) and standing height using a stadiometer (Holtain, Crymych, United Kingdom). Weight, height and BMI were compared to reference standards to generate age- and sex-specific Z scores[9]. Skinfold thickness was measured at the triceps and subscapular sites with a skinfold caliper (Holtain) to estimate subcutaneous fat stores using prediction equations adapted for children and adolescents[18,19]. Mid-upper arm circumference and triceps skinfold thickness measures were used to calculate upper arm muscle area and upper arm fat area[20]. Resultant areas were compared

with reference data from the National Center for Health Statistics to generate the Z scores[21]. At baseline, pubertal status according to the criteria of Tanner[22] was determined using a validated self-assessment questionnaire[23].

Dietary intake was estimated as the average of three 24-hour recalls at baseline by interview using visual aids for portion size (Nutrition Counseling Enterprises, Framingham, MA) and analyzed (Minnesota Nutrition Data System, Minneapolis, MN) for vit D and calcium expressed as percent Recommended Dietary Allowance (RDA)[24].

Adherence was also assessed by questionnaire at 6- and 12-weeks and phone calls at weeks 1, 3, 5, 8, and 10. Subjects were interviewed at each visit documenting intensity and frequency of adverse events. Socio-demographic information was obtained by questionnaire.

Biochemistry and hematology

Serum 25(OH)D was determined at all study visits using liquid chromatography tandem mass spectrometry (Clinical Laboratory, CHOP, [CHOP]) with intra and inter assay coefficients of variation (CV) below 7%. Bioavailable 25(OH)D (ng/mL), defined as the serum 25(OH)D that is not bound to vit D binding protein (VDBP) or to albumin, and bioavailable/total 25(OH)D (%) were calculated according to Powe et al[25]. Serum 1,25 dihydroxyvitamin D (1,25(OH)D) and intact parathyroid hormone (PTH) were assessed at baseline and 12 weeks by radioimmunoassay with radioiodinated tracer (Heartland Assays, Inc. Ames, IA). Inter and intra assays CVs were 12.6% and 9.8% for 1,25(OH)D and 2.7% and 4.3% for PTH, respectively. At all visits serum magnesium was assessed using standard techniques (CHOP). VDBP was assessed at baseline and 12 weeks by enzyme linked immunosorbent assay (R&D Systems, Inc, Minneapolis, MN) with inter and intra assay CVs below 10%. Safety and other assessments were conducted at all visits (complete blood count (CBC) with differential, phosphorus and fetal hemoglobin (fetal hemoglobin only in SCD-SS)) and baseline and 12 weeks (comprehensive metabolic panel, gamma glutamyl transferase and high-sensitivity C-reactive protein (HS-CRP)) according to standardized techniques. Spot urines were collected at all study visits for calcium and creatinine (CHOP).

Statistical analyses

All variables were tested for normality and nonparametric tests were used as appropriate. At baseline, differences between groups (SCD vs. control), at different doses (SCD vs. control at 4,000 IU; SCD vs. control at 7,000 IU) and within group at different doses (4,000 vs. 7,000 IU in SCD; 4,000 vs. 7,000 IU in controls) were determined using a Student’s t test or Wilcoxon’s rank-sum test for continuous variables and Fisher’s exact or chi-square test for categorical variables. Longitudinal-mixed-effects (LME) analyses[26] were used to examine change over time and whether patterns of change were different between the two groups and two vit D doses. These analyses were made using the intention-to-treat model where all subjects are included regardless of adherence to the study protocol. Similar to multiple linear regression analysis, LME analysis allows for multiple observations per subject. LME assumes that observations measured from the same subject are dependent and, therefore, the regression coefficients vary across subjects and are considered to be random. Also, it allows for unequal intervals between visits, uses data from all subjects, even when some study

visits were missed, and accommodates both fixed and random effects. Parameter estimates, as in regression analysis, indicate the contribution of the independent variable to the model. For these LME analyses which controlled for baseline value, the subject or dose group was treated as a random effect and measurement and time as fixed effects. All statistical analyses were performed by using STATA 12.0 (Stata Corp, College Station, TX). The results were considered significant at $P<0.05$ (unless otherwise indicated), and data are presented as means ± SDs (normal distribution) or medians and ranges (skewed distribution).

RESULTS

Forty-four subjects were enrolled, 21 (5.1 to 16.0 y) with SCD-SS and 23 (5.7 to 17.0 y) healthy subjects. Subject characteristics are presented in Table 1. Overall, growth status was suboptimal in children with SCD-SS as indicated by negative Z scores for height, weight and BMI. Nutritional status assessed by percent body fat and Z scores for upper arm muscle and fat areas was significantly lower in children with SCD-SS compared to healthy subjects. Median dietary intake of vit D and calcium was low, with half consuming ≤31% and ≤62% RDA, respectively[24].

In both children with SCD-SS and healthy subjects, after 12-weeks of supplementation, both D_3 doses were safe (Table 2). No subject had a study defined safety event of elevated serum calcium and elevated serum 25(OH)D. There was no change in calcium, magnesium, phosphorus, glucose, albumin, alkaline phosphatase, gamma-glutamyl transferase, or urine calcium/creatinine ratio over the 12 weeks.

For both children with SCD-SS and healthy controls, vit D status by dose group at each visit is shown in Table 3. At baseline 95% of subjects with SCD-SS and 87% of healthy controls had suboptimal vit D status (<32 ng/ml). The mean 25(OH)D at baseline was 19.2 ± 7.2 in subjects with SCD-SS and 22.3 ± 9.3 in healthy subjects. After 12-weeks of supplementation, the mean increase in 25(OH)D was 25.6 ± 22.3 ng/ml in subjects with SCD-SS and 20.5 ± 17.5 ng/ml in healthy subjects (both $p<0.05$) and neither group achieved the a priori efficacy criterion of 25(OH)D ≥ 32 ng/ml in >80% of subjects (45% in SCD-SS and 63% in controls). However for both subjects with SCD-SS and healthy subjects by 12-weeks, deficient (< 20 ng/ml) vit D status was eliminated only in those receiving 7,000 IU/d. In both groups, the significant increase in 25(OH)D with supplementation was accompanied by significant (all $p<0.05$) increases in bioavailable 25(OH)D (SCD-SS: +7.8 ± 8.5 ng/ml; Controls: +5.5 ± 5.8 ng/ml), 1,25(OH)D (SCD-SS: +15.9 ± 13.5 pg/ml; Controls: +16.3 ± 17.7 pg/ml), and decrease in PTH (SCD-SS: −10.4 ± 15.9 pg/ml; Controls: −9.5 ± 17.3 pg/ml). However, the proportion of the total 25(OH)D that was bioavailable did not change. In subjects with SCD-SS and healthy subjects, estimated adherence to supplementation was 73% and 74%, respectively, using the biweekly phone calls and 84% and 90%, respectively, from questionnaires with no differences between groups in any measure of adherence.

Hematologic and inflammatory status for subjects with SCD-SS and healthy controls by dose group at each visit is presented in Table 4. For subjects with SCD-SS, by 12-weeks there was a significant (all $P<0.05$) increase in fetal hemoglobin, decrease in HS-CRP, and reduction in the percentage of subjects with a elevated (> 400 × 103/μL) platelet count (79%

at baseline vs. 66% at 12-weeks). There was a trend (P=0.08) for fetal hemoglobin to increase in those receiving 7,000 IU/d but not 4,000 IU/d vit D_3. At baseline, 8 out of 21 subjects with SCD-SS (38%) were on hydroxyurea and no subject changed status (on/off hydroxyurea) throughout the 12-week intervention.

DISCUSSION

Suboptimal vit D status was prevalent in African American children and young adults with SCD-SS and healthy controls. Combined at baseline 91% of subjects had suboptimal vit D status (serum 25(OH)D <32 ng/ml) with 50% in deficient range (<20 ng/ml). Daily oral high dose D_3 supplementation of 4,000 and 7,000 IU was safe and well tolerated. In both SCD-SS and controls by 12-weeks, both doses significantly increased 25(OH)D; however deficient (< 20 ng/ml) vit D status was eliminated only in those receiving 7,000 IU/d. Other measures of vit D status improved with an increase in 1,25(OH)D and decrease in PTH. Collectively, these findings suggest daily high dose vit D supplementation for African American children and young adults with SCD-SS and healthy subjects was safe, effective and required to ensure no subject had deficient vit D status. It is possible that the vit D supplemental dose to achieve optimal response as indicated by serum 25(OH)D in all subjects in both group is higher than 7,000 IU/d. Additional research is needed to investigate this possibility.

Of the few available, most studies combine SCD genotypes when estimating prevalence of suboptimal vit D status. Data from Rovner et al.[7] published in 2008 in children with SCD-SS (ages 5 to 18 years) from the same region reported a high prevalence with 93% with a 25(OH)D concentration <30 ng/ml. Our results support the finding that suboptimal 25(OH)D status remains common in unsupplemented children and young adults with SCD-SS, with 95% at baseline having a 25(OH)D <32 ng/ml. Low 25(OH)D in SCD may be due to a combination of factors such as low vit D intake, skin pigmentation, inadequate sunlight exposure or unknown SCD associated factors. These findings highlight the need to determine the vit D supplementation dose that safely results in optimal year round serum 25(OH)D in SCD-SS. Additionally, studies are needed to determine if prevalence estimates of suboptimal vit D status differ by SCD genotype or other geographical regions.

The doses of vit D_3 chosen for this study were based upon several studies. In healthy adults, 3600 to 4200 IU/d of vit D_3 were required to sustain 25(OH)D concentrations of >32 ng/mL[13]. In adult men, Heaney et al.[27] demonstrated that for every microgram increment in vit D_3 supplement, there was an increase of 0.28 ng/ml in serum 25(OH)D concentration. Similarly, Weaver and Fleet[28] estimated that a dose of approximately 2000 IU/d for African American youth was needed to achieve serum 25(OH)D of 32 ng/ml. A 6-month, randomized, placebo controlled of vit D_3 supplementation study in healthy African American and Caucasian adults found a daily dose of 3,440 IU was necessary for most subjects to attain 25(OH)D >30 ng/ml; for those values <22 ng/mL, 5000 IU was necessary[29]. Data from two previous studies in children, adolescents and young adults with SCD-SS[7,30] showed an average 25(OH)D value of 12.6 ng/mL. Therefore, in order to achieve a serum 25(OH)D concentration of 32 ng/ml, a minimum dose of 2771 IU/d is needed based on Heaney et al.[27]. However, the prediction models estimate the vit D intake

needed to achieve an average serum 25(OH)D of 32 ng/ml in healthy subjects, and not the amount needed to assure an optimum concentration in the majority of subjects. In healthy adults, a vit D_3 dose of 4000 IU/d resulted in a minimum 25(OH)D plateau concentration of 28 ng/ml[31]. Thus, due to SCD status, varied medications, likely low dietary intake of vit D, and darker skin pigmentation in many subjects with SCD, we tested doses of 4000 and 7000 IU/d in our sample of predominantly African American youth living with SCD-SS. We hypothesized that these supplementation dose levels would assure that all, or nearly all subjects will achieve a 25(OH)D concentration >32 ng/mL. Results showed that although 25(OH)D concentrations increased significantly in both subjects with SCD-SS or controls, neither group achieved the a priori efficacy criterion of 25(OH)D ≥ 32 ng/ml in >80% of subjects. Of note, by 12-weeks, deficient (< 20 ng/ml) vit D status was eliminated in both groups only in those receiving 7,000 IU/d.

Although case reports in children and adults with SCD illustrate the resolution of vit D deficiency with high dose vit D_2[32] (3 times/week) and vit D_3[33] (2 times/week) supplementation, prospective studies with larger sample sizes investigating optimal dosing regimens, safety and efficacy of vit D for sufficient 25(OH)D status in this population are sparse. In 14 vit D deficient adults with SCD (11 hemoglobin SS; 3 hemoglobin SC), Adewoye et al.[34] administered 50,000 IU/week vit D_2 (equivalent to 7,143 IU/day) for 8 weeks and then biweekly for 44 weeks. Results showed an increase in 25(OH)D concentrations to 34.6 ± 11 ng/ml. However this study was not randomized, double-blinded or placebo controlled and it did not report the percentage of subjects in the insufficient and optimal ranges post-treatment. Three studies of vit D supplementation have been conducted in children with SCD[35–37]. The earliest work from the 1960s in children with SCD-SS, ages 2 to 12 years, focused on disease progression, giving vit D (D_2 or D_3 not specified) in combination with other drugs and did not report 25(OH)D concentrations[35]. More recently, Osunkwo et al.[37] randomized 46 children and young adults with SCD (29 hemoglobin SS, 5 hemoglobin SC, 2 sickle beta zero thalassemia and 10 sickle beta plus thalassemia) aged 7- to 21-years to a weekly vit D_3 dose based on weight ranging from 40,000 to 100,000 for 6 weeks or placebo with monitoring extended to 6 months. At baseline, 83% and 53% of subjects were vit D insufficient and deficient, respectively. A significant increase in 25(OH)D and decrease in pain days/week were reported, however the percentage of subjects in each vit D status category after supplementation was not assessed. In a double-blind study focused on post-operative anesthesia Shams et al.[36] randomized 58 children with SCD (42 hemoglobin SS, 5 hemoglobin SC, 11 sickle beta plus thalassemia) undergoing circumcision to 400 IU/day vit D (D_2 or D_3 not specified) for 6 months before surgery or no vit D. Those in the vit D group showed a delay in post-operative analgesic request, less total analgesic requirement and fewer complications. Although the authors demonstrated a significant increase in 25(OH)D with supplementation in the vit D vs. no vit D groups, the percentage of subjects with 25(OH)D concentrations in the optimum, insufficient and deficient ranges was not reported either pre- or post-operative. Collectively data from these previous vit D supplementation studies in SCD have combined SCD genotypes which does not allow for assessment of individual disease states. Additionally, these studies did not assess the vit D dose (either D_2 or D_3) needed to safely assure an optimum 25(OH)D concentration in the majority of subjects. Our study is the first test daily vit D_3 supplementation at various doses

in children and young adults with SCD-SS. We recommend consideration of daily dosing as an approach for achieving and maintaining 25(OH)D status in the SCD care setting. Based upon our results, 7,000 IU/d is needed to eradicate deficient status and it is possible that higher doses are needed to assure optimum 25(OH)D concentrations in the majority of subjects.

In the present study, subjects with SCD-SS had a significant increase in fetal hemoglobin and decrease in HS-CRP by 12-weeks. The mechanisms for these findings are unclear, however may be related to independent associations between vit D status and inflammation and anemia[38]. Timms et al.[39] found an inverse relationship between 25(OH)D and CRP concentrations and showed that 50,000 IU/month vit D_3 supplementation for three months corrected this abnormality. Vit D deficient adults have lower hemoglobin concentrations and a greater risk of anemia compared to those with optimal 25(OH)D status[40]. Thus, it is possible that in the present study vit D modulated the inflammatory and/or anemic status of subjects with SCD-SS and warrants further study.

In summary, suboptimal vit D status was prevalent in both healthy children and young adults and those with SCD-SS. Both daily vit D_3 doses were safe and effective in increasing serum 25(OH)D in both groups, although neither achieved the a priori efficacy criterion of 25(OH)D ≥ 32 ng/ml in >80% of subjects. However, deficient (< 20 ng/ml) vit D status was eliminated in both groups only in those receiving 7,000 IU/d. Modest improvements in hematology and inflammatory status were seen with supplementation. Collectively, these findings highlight the need for full scale randomized double blind placebo controlled trials to test the impact of optimal D_3 supplementation on clinically important outcomes in children and young adults with SCD-SS and their healthy counterparts.

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Table 1

Characteristics of subjects with SCD-SS and Controls at baseline[a]

	All	SCD	Controls
N	44	21	23
4,000 IU	23	12	11
7,000 IU	21	9	12
Age (yr)	10.5 ± 3.9[b]	10.8 ± 4.0	10.3 ± 3.9
4,000 IU	10.5 ± 4.0	11.2 ± 3.7	9.7 ± 4.3
7,000 IU	10.6 ± 3.9	10.2 ± 4.5	10.9 ± 3.5
Gender (% male)	50	43	57
Season (%)			
Summer	59	66	52
Fall/Winter	18	24	13
Spring	23	10	35
Height Z score	−0.1 ± 1.1	−0.5 ± 1.2	0.4 ± 1.0*
4,000 IU	−0.2 ± 1.2	−0.7 ± 1.3	0.3 ± 1.0*
7,000 IU	0.2 ± 1.0	−0.2 ± 0.9	0.5 ± 1.0
Weight Z score	0.1 ± 1.4	−0.7 ± 1.2	0.8 ± 1.1*
4,000 IU	−0.2 ± 1.5	−1.1 ± 1.1	0.9 ± 1.0*
7,000 IU	0.4 ± 1.2	−0.1 ± 1.1	0.7 ± 1.3
BMI Z score	0.1 ± 1.3	−0.6 ± 1.1	0.7 ± 1.1*
4,000 IU	−0.2 ± 1.3	−1.0 ± 0.9	0.8 ± 1.1*
7,000 IU	0.4 ± 1.2	−0.1 ± 1.1**	0.6 ± 1.2
UAMA Z score	0.2 ± 1.7	−0.6 ± 1.2	1.0 ± 1.8*
4,000 IU	−0.2 ± 1.4	−1.0 ± 1.0	0.8 ± 1.2*
7,000 IU	0.7 ± 2.0	−0.1 ± 1.3	1.3 ± 2.3
UAFA Z score	−0.1 ± 1.4	−0.8 ± 0.7	0.6 ± 1.6*
4,000 IU	−0.2 ± 1.1	−1.0 ± 0.4	0.6 ± 1.0*
7,000 IU	0.1 ± 1.8	−0.5 ± 0.9	0.6 ± 2.1
Body fat (%)	16.3 ± 8.2	13.7 ± 6.6	18.8 ± 8.8*
Pubertal stage (#)			
1	4	4	5
2	1	0	1
3	7	4	3
4	5	2	3
5	5	2	3
Dietary intake			
Vitamin D (IU/d)	181 [14, 528][c,1]	167 [14, 365][2]	190 [35, 528]
Vitamin D (% RDA)	31 [2, 88][1]	28 [2, 61][2]	33 [6, 88]

	All	SCD	Controls
Calcium (mg/d)	740 [270, 1607][1]	631 [355, 1380][2]	857 [270, 1607]*
Calcium (% RDA)	62 [27, 155][1]	52 [27, 106][2]	67 [27, 155]

[a] SCD-SS, type SS sickle cell disease; BMI, body mass index; UAMA, upper arm muscle area; UAFA, upper arm fat area; RDA, Recommended Dietary Allowances. Spring (April–May), Summer (June–August) and Fall/Winter (September–January). Group differences at baseline (SCD vs. control and 4,000 vs. 7,000) were determined using a Student's t test or Wilcoxon's rank-sum test for continuous variables and Fisher's exact or chi-square test for categorical variables.

* P<0.05, Controls vs. SCD.

** P<0.05, 4,000 vs. 7,000 IU.

[b] Mean ± SD (all such values)

[c] Median; range in brackets [all such values]

[1] n=43

[2] n=20

Table 2

Laboratory values for subjects with SCD-SS and Controls by dose group at each visit[a]

	SCD-SS		Controls	
	Baseline	**12-weeks**	**Baseline**	**12-weeks**
N	21	20	23	19
4,000 IU	12	11	11	10
7,000 IU	9	9	12	9
Calcium (mg/dL)	9.4 ± 0.3[b]	9.4 ± 0.3	9.4 ± 0.4	9.5 ± 0.3
4,000 IU	9.4 ± 0.3	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.4
7,000 IU	9.5 ± 0.3	9.5 ± 0.3	9.6 ± 0.4	9.4 ± 0.3
Magnesium (mg/dL)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.1	1.9 ± 0.1
4,000 IU	1.9 ± 0.2	1.9 ± 0.1	1.9 ± 0.1	1.9 ± 0.1
7,000 IU	1.8 ± 0.1	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.1
Phosphorous (mg/dL)	5.1 ± 0.4	5.1 ± 0.4	4.9 ± 0.5	4.7 ± 0.4
4,000 IU	5.0 ± 0.4	5.1 ± 0.4	4.9 ± 0.6	4.8 ± 0.5
7,000 IU	5.1 ± 0.4	5.2 ± 0.4	4.9 ± 0.5	4.7 ± 0.4
Glucose (mg/dL)	76.4 ± 6.2	78.1 ± 4.8	79.9 ± 7.1	80.8 ± 8.6
4,000 IU	75.7 ± 6.2	78.0 ± 5.6	79.7 ± 7.7	85 ± 9.4
7,000 IU	77.4 ± 6.4	78.3 ± 3.8	80.1 ± 6.7	76.6 ± 5.3
Albumin (g/dL)	4.5 [4.2, 5.0][c]	4.5 [4.2, 5.1]	4.4 [3.9, 5.0]	4.2 [3.6, 4.9]
4,000 IU	4.5 [4.4, 5.0]	4.5 [4.3, 5.1]	4.3 [3.9, 5.0]	4.2 [3.6, 4.8]
7,000 IU	4.5 [4.2, 5.0]	4.5 [4.2, 4.9]	4.5 [4.1, 4.9]	4.3 [3.9, 4.9]
Alkaline phosphatase (U/L)	162 [79, 272]	159 [86, 218]	244 [51, 393]	231 [64, 374]
4,000 IU	173 [23, 272]	167 [116, 187]	226 [51, 359]	187 [69, 374]
7,000 IU	153 [79, 252]	147 [86, 218]	258 [73, 393]	267 [64, 360]
GGT (U/L)	29.2 ± 13.1	27.2 ± 10.6	24.0 ± 8.2	23.9 ± 7.7
4,000 IU	33.3 ± 14.0	28.3 ± 10.9	24.0 ± 9.4	23.5 ± 8.5
7,000 IU	23.9 ± 10.4	25.8 ± 10.7	24.1 ± 7.2	24.3 ± 7.2
Urine calcium/creatinine ratio (mg/dL)	0.02 [0.007, 0.15]	0.02 [0.008, 0.17]	0.01 [0.003, 0.21][1]	0.01 [0.005, 0.12][4]
4,000 IU	0.02 [0.01, 0.15]	0.03 [0.01, 0.17]	0.02 [0.004, 0.11][2]	0.02 [0.009, 0.12][5]
7,000 IU	0.02 [0.007, 0.05]	0.02 [0.008, 0.02]	0.01 [0.003, 0.21][3]	0.01 [0.005, 0.08]

[a] SCD-SS, type SS sickle cell disease; GGT, gamma-glutamyl transferase. Longitudinal-mixed-effects (LME) analyses were used to examine change over time and whether patterns of change were different between the two groups and two vit D doses. These analyses were made using the intention-to-treat model where all subjects are included regardless of adherence to the study protocol. For these LME analyses which controlled for baseline value, the subject or dose group was treated as a random effect and measurement and time as fixed effects. No differences were detected.

[b] Mean ± SD (all such values)

[c] Median; range in brackets [all such values]

[1] n=21

[2] n=10

[3] n=11

[4] n=18

[5] n=9

Table 3

Vitamin D status for subjects with SCD-SS and Controls by dose group at each visit[a]

	SCD			Controls		
	Baseline	**6-weeks**	**12-weeks**	**Baseline**	**6-weeks**	**12-weeks**
N	21	21	20	23	20	19
4,000 IU	12	12	11	11	10	10
7,000 IU	9	9	9	12	10	9
Total 25(OH)D (ng/ml)	18.2 [4.7, 32.2][b]	44.6 [15.1, 106]*	30.3 [8.4, 108]**	24 [7.4, 46.4]	38.7 [19.3, 77.3]†	36.3 [18.4, 75.3]‡
4,000 IU	17.7 [4.7, 28.9]	38.2 [15.1, 91.4]*	28.9 [8.4, 82.6]**	24.4 [8.0, 34.2]	42.2 [19.3, 69.5]†	40.9 [18.4, 72.8]‡
7,000 IU	18.8 [12.7, 32.2]	49.6 [19.4, 106]*	48.8 [21.3, 108]**	20.4 [7.4, 46.4]	38.7 [25.4, 77.3]†	34.1 [20.6, 75.3]‡
Total 25(OH)D < 20 ng/ml (%)	57	10*	5**	44	5†	5‡
4,000 IU	58	8*	9**	36	10†	10‡
7,000 IU	56	11*	0**	50	0†	0‡
Total 25(OH)D < 32-20 ng/ml (%)	38	19	50	43	30	32
4,000 IU	42	25	55	46	20	20
7,000 IU	33	11	44	42	40	44
Total 25(OH)D ≥ 32 ng/ml (%)	5	71*	45**	13	65†	63‡
4,000 IU	0	67*	36**	18	70†	70‡
7,000 IU	11	78*	56**	8	60†	56‡
Bioavailable 25(OH)D (ng/ml)	4.1 [1.2, 11.4][1]		7.4 [3.0, 36.2]**[3]	5.2 [2.3, 13.5]		10.1 [2.7, 23.3]‡
4,000 IU	3.0 [1.2, 11.4][2]		6.0 [3.0, 30.9]**	4.3 [2.3, 10.6]		9.2 [2.7, 23.3]‡
7,000 IU	4.1 [3.0, 10.3]		11.7 [3.5, 36.2]**[4]	5.6 [2.5, 13.5]		11.1 [2.9, 21.3]‡
Bioavailable/Total 25(OH)D (%)	24.9 [10.9, 39.4][1]		26.4 [12.3, 38.8][3]	28.3 [8.4, 40.5]		28.3 [7.3, 38.3]
4,000 IU	25.9 [11.3, 39.4][2]		26.4 [12.3, 37.4]	25.0 [8.4, 39.8]		24.7 [7.3, 38.3]
7,000 IU	23.9 [10.9, 33.9]		28.8 [16.2, 38.8][4]	28.7 [13.5, 40.5]		30.2 [14.2, 36.2]
1,25(OH)D (pg/ml)	35.8 [22.3, 58.4]		50.2 [25.8, 94.0]**	38.6 [14.6, 74.4]		50.7 [25.9, 95.5]‡
4,000 IU	38.0 [25.5, 58.4]		51.7 [25.8, 94.0]**	38.7 [14.6, 74.4]		51.6 [25.9, 95.5]‡
7,000 IU	34.6 [22.3, 48.2]		49.4 [26.1, 77.1]**	38.5 [21.0, 57.1]		50.7 [29.6, 70.2]‡

	SCD			Controls		
	Baseline	**6-weeks**	**12-weeks**	**Baseline**	**6-weeks**	**12-weeks**
VDBP (μmol/L)	1.7 [1.0, 5.4][1]		1.6 [0.9, 4.4][3]	1.6 [0.8, 6.4]		1.4 [0.9, 7.4]
4,000 IU	1.7 [1.0, 4.6][2]		1.6 [1.0, 4.4]	1.5 [0.8, 6.4]		1.6 [0.9, 7.4]
7,000 IU	1.8 [1.1, 5.4]		1.6 [0.9, 3.1][4]	1.6 [0.9, 4.1]		1.4 [1.1, 3.8]
PTH (pg/ml)	36.4 [22.8, 58.5]		25.0 [16.6, 53.1]**	38.5 [16.9, 74.5]		27.3 [18.1, 46.0]‡
4,000 IU	35.2 [23.9, 58.5]		27.6 [17.0, 53.1]	38.7 [20.7, 61.2]		29.7 [20.1, 40.2]‡
7,000 IU	39.1 [22.8, 55.8]		22.8 [16.6, 35.5]**	36.5 [16.9, 74.5]		22.5 [18.1, 46.0]‡

[a] SCD-SS, type SS sickle cell disease; 25(OH)D, 25-hydroxyvitamin D; 1, 25(OH)D, 1,25-dihydroxyvitamin D; VDBP, vitamin D binding protein, PTH, parathyroid hormone. Longitudinal-mixed-effects (LME) analyses were used to examine change over time and whether patterns of change were different between the two groups and two vit D doses. These analyses were made using the intention-to-treat model where all subjects are included regardless of adherence to the study protocol. For these LME analyses which controlled for baseline value, the subject or dose group was treated as a random effect and measurement and time as fixed effects.

* P<0.05, 6-weeks vs. baseline in SCD,

** P<0.05, 12-weeks vs. baseline in SCD,

† P<0.05, 6-weeks vs. baseline in Controls,

‡ P<0.05, 12-weeks vs. baseline in Controls.

[b] Median; range in brackets [all such value]

[1] n=20

[2] n=11

[3] n=19

[4] n=8

Table 4

Hematologic and inflammatory status for subjects with SCD-SS and Controls by dose group at each visit[a]

	SCD			Controls		
	Baseline	**6-weeks**	**12-weeks**	**Baseline**	**6-weeks**	**12-weeks**
N	19	19	16	22	19	18
4,000	10	10	8	10	9	9
7,000	9	9	8	12	10	9
HgbF (%)	12.4 ± 5.8[b]	12.7 ± 5.9	14.0 ± 6.2[*2]			
4,000 IU	9.9 ± 5.3	10.5 ± 5.5	11.5 ± 5.4[3]			
7,000 IU	15.1 ± 5.4	15.1 ± 5.7	16.1 ± 6.3[¥]			
Hematocrit (%)	25.9 ± 3.1	25.9 ± 3.0	25.7 ± 3.4	39.8 ± 3.1	40.4 ± 3.3	40.0 ± 4.2
4,000 IU	24.9 ± 3.3	25.4 ± 3.2	24.4 ±3.6	40.5 ± 3.7	40.5 ± 3.5	40.9 ± 5.5
7,000 IU	27.0 ± 2.6	26.4 ± 2.8	26.9 ± 3.0	39.3 ± 2.6	40.3 ± 3.2	40.0 ± 1.9
Hemoglobin (g/dl)	8.4 ± 1.0	8.4 ± 1.0	8.2 ± 1.1	13.0 ± 1.1	13.2 ± 1.0	13.0 ± 1.4
4,000 IU	8.1 ± 1.2	8.2 ± 1.0	8.0 ± 1.0	13.1 ± 1.2	13.2 ± 1.1	13.2 ± 1.8
7,000 IU	8.7 ± 0.8	8.6 ± 0.9	8.6 ± 1.0	13.0 ± 1.1	13.2 ± 1.1	12.7 ± 0.7
MCH	30.1 ± 3.4	30.1 ± 3.3	30.1 ± 3.4	27.2 ± 2.1	27.1 ± 2.1	26.8 ± 2.0
4,000 IU	29.6 ± 4.1	29.6 ± 3.9	30.0 ± 4.5	26.3 ± 2.5	26.5 ± 2.5	26.3 ± 2.4
7,000 IU	30.6 ± 2.7	30.7 ± 2.5	30.2 ± 2.3	27.9 ± 1.4	27.7 ± 1.6	27.3 ± 1.3
MCHC (g/dl)	32.4 ± 1.0	32.4 ± 0.7	32.2 ± 1.0	32.7 ± 1.1	32.7 ± 0.9	32.5 ± 1.0
4,000 IU	32.4 ± 1.3	32.2 ± 0.9	32.5 ± 1.1	32.3 ± 1.2	32.7 ± 0.8	32.3 ± 0.8
7,000 IU	32.4 ± 0.7	32.6 ± 0.5	32.0 ± 0.8	33.0 ± 1.0	32.9 ± 1.0	32.7 ± 1.2
MCV (fL)	92.7 ± 9.2	93.0 ± 9.5	93.3 ± 9.8	83.0 ± 5.5	82.7 ± 5.9	82.6 ± 5.4
4,000 IU	91.0 ± 10.1	92.0 ± 11.5	92.0 ± 11.6	81.4 ± 6.4	81.0 ± 6.5	81.5 ± 6.6
7,000 IU	94.5 ± 8.1	94.2 ± 7.3	94.6 ± 8.1	84.3 ± 4.5	84.3 ± 5.1	83.7 ± 4.1
WBC (× 10^3/μL)	9.5 ± 2.3	9.7 ± 2.0	9.5 ± 1.8	5.3 ± 1.5	5.4 ± 1.7	5.7 ± 1.7[**]
4,000 IU	9.6 ± 2.8	9.8 ± 1.4	9.4 ± 1.8	5.5 ± 1.6	5.8 ± 1.7	6.4 ± 1.8[**]
7,000 IU	9.5 ± 1.7	9.5 ± 2.7	9.6 ± 1.9	5.1 ± 1.4	5.1 ± 1.8	5.0 ± 1.1
RBC (× 10^6/μL)	2.8 ± 0.5	2.8 ± 0.5	2.8 ± 0.5	4.8 ± 0.5	4.9 ± 0.4	4.8 ± 0.5
4,000 IU	2.8 ± 0.7	2.8 ± 0.7	2.7 ± 0.8	5.0 ± 0.5	5.0 ± 0.5	5.0 ± 0.5

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	SCD			Controls		
	Baseline	**6-weeks**	**12-weeks**	**Baseline**	**6-weeks**	**12-weeks**
7,000 IU	2.9 ± 0.2	2.8 ± 0.3	2.8 ± 0.2	4.7 ± 0.5	4.8 ± 0.4	4.7 ± 0.4
HS-CRP (mg/L)	3.0 ± 2.6		2.0 ± 1.7*	1.1 ± 1.5		1.2 ± 1.9
4,000 IU	2.0 ± 2.0[1]		1.3 ± 1.0	0.7 ± 0.7		1.0 ± 1.2
7,000 IU	4.0 ± 2.7		2.8 ± 2.1*	1.5 ± 1.9		1.4 ± 2.5
Platelets (× 10^3/μL)	522 ± 158	522 ± 143	457 ± 143*	304 ± 64	316 ± 73	311 ± 72
4,000 IU	599 ± 174	586 ± 173	482 ± 188*	295 ± 61	322 ± 80	329 ± 87
7,000 IU	436 ± 80†	451 ± 39‡	433± 87	310 ± 68	311 ± 71	294 ± 54

[a] SCD-SS, type SS sickle cell disease; HgbF, fetal hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; WBC, white blood cells; RBC, red blood cells; HS-CRP, high-sensitivity C-reactive protein. Longitudinal-mixed-effects (LME) analyses were used to examine change over time and whether patterns of change were different between the two groups and two vit D doses. These analyses were made using the intention-to-treat model where all subjects are included regardless of adherence to the study protocol. For these LME analyses which controlled for baseline value, the subject or dose group was treated as a random effect and measurement and time as fixed effects.

* P<0.05, 12-weeks vs. baseline in SCD,

¥ trend P=0.08,

** P<0.05, 12-weeks vs. baseline in Controls,

† P<0.05, 7,000 vs. 4,000 at baseline,

‡ P<0.05, 7,000 vs. 4,000 at 6-weeks.

[b] Mean ± SD (all such values)

[1] n=9

[2] n=15

[3] n=7