Treatment of vitamin D deficiency in transfusion-dependent thalassemia

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The survival of patients with thalassemia major has progressively improved with advances in therapy; however, osteoporosis remains a frequent, unresolved issue [1]. Adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk [2]. Vitamin D insufficiency is reported in the majority of patients with thalassemia in the USA [3] and elsewhere [4–10], despite routine prescription of 400–1,000 IU vitamin D per day. In this study, assessment of serum 25-hydroxy vitamin D (25-OH D) levels in 96 patients with thalassemia revealed that 70 (73%) were either deficient (<20 ng/ml, 43%) or insufficient (20–29 ng/ml, 30%). Significantly more transfusion-independent patients were deficient compared with the transfusion-dependent group (60% versus 33%, $P = 0.014$). Supervised administration of high-dose (50,000 IU) oral vitamin D_2 every 3 weeks during transfusion visits in 32 transfusion-dependent patients increased the 25-OH D level from 18.4 to 24.2 ng/ml ($P < 0.001$) over a 4-month period. Each dose of vitamin D_2, given at 3-week intervals, increased 25-OH D levels by 1.4 ± 2.0 ng/ml. These results show that vitamin D deficiency remains widespread despite daily low-dose supplementation. Supervised high-dose oral vitamin D supplementation is a safe and noninvasive method for predictable improvement of vitamin D status in thalassemia.

The risk of vitamin D deficiency in thalassemia increases with age [9,10], and older patients with thalassemia have significantly worse vitamin D status compared with age-matched healthy controls [10]. One-third of healthy adults consuming vitamin D-fortified milk and multivitamin supplementation remain vitamin D-deficient [11]. Similarly, despite greater awareness and routine prescription of daily vitamin D, the problem of vitamin D deficiency in thalassemia remains intractable. The alternative to daily supplementation is intermittent supervised therapy with high-dose vitamin D [12]. Oral therapy is desirable to maintain long term acceptance of the therapy. The objective of this study was to evaluate the effect of high-dose (50,000 IU) oral vitamin D_2 administered at the time of transfusion on serum levels of 25-OH D.

We screened 96 patients between 3.6 and 57.5 years of age (mean ± SD: 25.2 ± 12.9 years; Table I-online material) with various types of thalassemia for vitamin D status. Exactly half of this sample was male and 61 (64%) of the patients were transfusion-dependent. There were significantly more patients with Asian ethnic background in the transfusion-independent than in the transfusion-dependent category (80% vs. 62.3%, $P = 0.002$). Serum 25-OH D levels were sufficient in only 26 (27%) patients, whereas 41 (43%) were deficient and 29 (30%) were insufficient. There were no significant differences in age, gender, or season of sample collection between those with deficient and sufficient levels of 25-OH D. The mean parathyroid hormone level in patients with 25-OH D<20 ng/ml was 38.6 ± 21.4 pg/ml compared with 27.3 ± 12.6 pg/ml in those with 25-OH D ≥ 20 ng/ml ($P < 0.001$).

There was a trend toward a lower mean 25-OH D level among patients with Asian ethnic background (mean 22.4 ± 12.3 ng/ml) compared with Caucasian ethnic background (26.8 ± 9.7 ng/ml, $P = 0.12$). Additionally, deficient vitamin D status was significantly more prevalent in patients with Asian ethnic background than the Caucasian ethnic group (56% vs. 9.7%, $P = 0.002$). There was no difference in the mean 25-OH D level among patients with Hemoglobin H or Hemoglobin H Constant Spring disease (mean 22.2 ± 12.9 ng/ml), and those with other types of nontransfusion-dependent thalassemia (23.2 ± 12.9 ng/ml, $P = 0.82$), or transfusion-dependent thalassemia (24.6 ± 10.8 ng/ml, $P = 0.39$). However, a majority (60%) of the nontransfused group had deficient levels of 25-OH D compared with the transfusion-dependent group (32.8%, $P = 0.014$, Fig. 1).

Thirty-two transfusion-dependent patients with 25-OH D <30 ng/ml were placed on intermittent high-dose oral vitamin D_2 supplementation for a total of 66 unique supplementation periods. These patients received a mean of 5 (1–15) doses of 50,000 IU vitamin D_2 over 129 (14–521) days. The mean daily dose of vitamin D_2 delivered according to this protocol was 2,118 IU/day. The baseline 25-OH D level increased from 18.4 ± 5.9 ng/ml to 24.3 ± 8.8 ng/ml following supplementation ($P < 0.001$, Fig. 2). Administration of each dose of 50,000 IU vitamin D_2 increased serum 25-OH vitamin D by 1.4 ± 2.0 ng/ml. Regardless of the baseline vitamin D level or the duration of the supplement regimen, no 25-OH D level >80 ng/ml was observed over the course of the observation period.

There were 18 individuals who attained a 25-OH D level >30 ng/ml at the end of their supplementation period and continued daily supplementation of 400–1,000 IU vitamin D thereafter. When retested at an average of 8 months (1–21 months) later, the serum 25-OH D had dropped significantly and collectively for all but two of them, from a mean of 34.4 ± 3.7 to 26.9 ± 6.8 ng/ml ($P < 0.001$). The rate of decline was on an average 1.5 ng/ml per month. Hence, patients who had inadequate vitamin D status on screening were likely to require ongoing high-dose supplementation. In contrast, the

TABLE I. Baseline Characteristics of Subjects with Thalassemia ($n = 96$)

Mean age, years	25.2 (range: 3.6–57.5)
Gender	
Female	48
Male	48
Ethnic group, Asian	66 (69%)
Caucasian	23 (24%)
Other/mixed	7 (7%)
Type of thalassemia	
β or E,B thalassemia transfused	61 (63.5%)
β or E,B thalassemia non-transfused	13 (13.5%)
Hb H or H Constant Spring	22 (22.9%)
Mean 25-OH vitamin D (ng/ml)	23.9 (range: 5–68)
Mean Parathyroid hormone (pg/ml)	31.8 (range: 6–115)

Mean ± SD. Frequency (% of total or range provided) is given either in range or percentage.

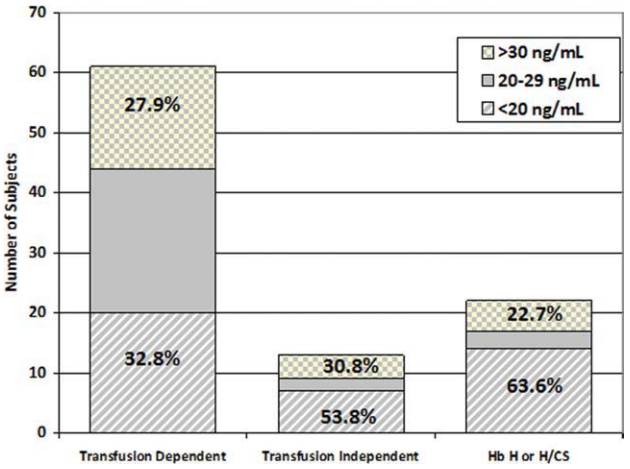

Figure 1. Categorization of patients with transfusion-dependent thalassemia ($n = 61$: β-thalassemia 43, E-β thalassemia 18), transfusion-independent ($n = 35$: β-thalassemia 8, E-β thalassemia 5, hemoglobin H or hemoglobin H Constant Spring disease 22) by baseline vitamin D level. Vitamin D sufficiency (serum 25-OH $D \geq 30$ ng/ml) is noted by hatched bars, insufficiency (20–29 ng/ml) by gray bars, and deficiency (<20 ng/ml) by striped bars. There was a significant difference in the prevalence of vitamin D deficiency by transfusion status ($P < 0.014$).

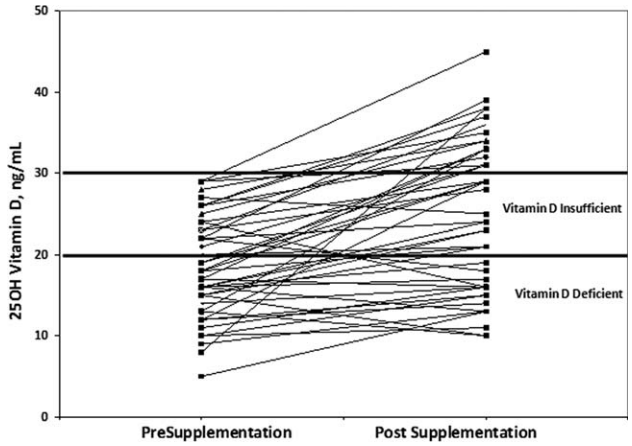

Figure 2. Serum 25-hydroxy vitamin D levels before and after supplementation with intermittent high-dose oral vitamin D_2 (50,000 IU given every 3 weeks) in transfusion-dependent thalassemia (32 patients, 66 unique observations). The average length of supplementation was 130 ± 93 days. The two horizontal lines represent vitamin D deficiency (<20 ng/ml) and insufficiency (<30 ng/ml).

35 patients who had normal vitamin D status on screening did not show a similar decline in 25-OH D when maintained on daily oral low-dose supplementation. Twenty (57%) had a decrease in their 25-OH D level by ≥5 ng/ml, whereas 15 (43%) had either stable or higher level during follow up.

Our data demonstrate that the problem of inadequate vitamin D status in thalassemia has persisted despite routine daily supplementation of 400–1,000 IU vitamin D. Though hyperparathyroidism in thalassemia is rare, vitamin D deficiency was correlated with increased parathyroid hormone level in this and a previous study [12]. Identifying the optimal strategy for replacing vitamin D in patients with thalassemia is critical because adequate circulating levels of vitamin D are essential for optimal skeletal health and reducing fracture risk [13]. A significant negative correlation exists between 25-OH D levels and spine bone mineral density in thalassemia [1]. Moreover, the association between vitamin D deficiency and myocardial iron deposition and cardiac ejection fraction in thalassemia is of increasing interest [4,14]. Patients with elevated myocardial iron were noticed to have a 40% higher level of serum parathyroid hormone [4]. Removing this modifiable risk factor may improve long-term bone health and quality of life in aging patients with thalassemia.

In our experience, the intermittent high-dose supplementation with oral 50,000 IU vitamin D_2 every 3 weeks proved to be an effective and safe strategy for increasing 25-OH D levels. One other group has studied the efficacy of high-dose vitamin D_3 (10,000 IU/kg) in thalassemia given as a single intramuscular injection. Although a majority of the patients showed an improvement in 25-OH D level to >20 ng/ml, the effect did not persist at 6 months [12,15].

This observation is similar to our own data which suggest that repeated courses of high-dose vitamin D will be necessary for most individuals with thalassemia who are diagnosed with vitamin D deficiency. Even patients with normal vitamin D status on screening were at risk of developing insufficiency during followup visits during our study. Though seasonality and assay variability can affect measurements, we suggest that 25-OH D levels should be monitored annually in all patients with thalassemia.

A 4-month-period of supplementation proved inadequate to bring the 25-OH D to a level >30 ng/ml for many patients in our study. Since the average increment in serum level of 25 OH-D with each 50,000 IU dose of vitamin D_2 administered at 3-week-intervals was 1.4 ng/ml, a patient with a starting 25-OH D level of 10 ng/ml would require 14 or more doses to achieve sufficiency. Patients with severe deficiency may benefit from larger doses of vitamin D than used in this report. While both vitamin D_2 and vitamin D_3 are efficacious, the latter possesses three times more biological activity in maintaining serum 25-OH D levels [16]. Thus, the dose-effect of 50,000 IU vitamin D_2 observed by us may be replicated by a lower dose of vitamin D_3. The difference in potency is likely to be clinically unimportant since the supplement is being provided as repeated intermittent doses, instead of a single large dose.

Transfusion-independent patients, especially those with Hemoglobin H and Hemoglobin H Constant Spring disease, were at particularly high risk for vitamin D deficiency. These patients have fewer clinic visits and receive less nutritional counseling compared with transfusion-dependent patients. A combination of poor dietary and supplemental intake, darker skin, or less sun exposure could place them at increased risk for deficiency. Optimal strategies for vitamin D supplementation in nontransfused patients should be addressed in future studies.

The present study shows for the first time the efficacy and tolerability of intermittent high-dose oral vitamin D supplementation in thalassemia given in a simple, noninvasive regimen that is convenient and acceptable to patients. This regimen, provided at the time of transfusion, alleviates burden to the patient (daily dosing) and assures adherence for the clinician (supervised therapy). The safety of this regimen is demonstrated by the nontoxic levels of 25-OH D at the end of the period of supplementation. The average daily dose of vitamin D_2 used in this study (2,100 IU/day) is lower than the upper limit for children and adults, which was recently revised by the U.S. Institute of Medicine to 4,000 IU/day for all forms of vitamin D [13]. We recommend that 25-OH D levels should be monitored every 6 months in patients on high-dose supplementation to ensure adequacy of therapy and to monitor for toxicity.

Methods

Patients with thalassemia attending Children's Hospital & Research Center, Oakland (CHRCO) are routinely prescribed daily vitamin D 400–1,000 IU and checked for adequacy of vitamin D status every year. Beginning in January 2007, new treatment guidelines recommended supervised therapy with 50,000 IU of ergocalciferol (vitamin D_2) in the form of a gel capsule on the day of the transfusion (every 3 weeks) for patients with low vitamin D status. Blood samples were obtained at baseline and after 4–6 months of supplementation to calculate the rate of correction of serum 25-OH D level. If the 25-OH D level remained <30 ng/ml at the end of this period, an additional cycle of supplementation was begun. The post-supplementation 25-OH D level was obtained within 3 months of the last dose of vitamin D_2.

Data collected from chart review included age, gender, type of thalassemia, and number of doses of vitamin D supplement. The 25-OH D level was measured using a chemiluminescent immunoassay (ARUP, Salt Lake City, Utah), which quantifies the sum of 25-OH D_2 and 25-OH D_3. The serum 25-OH D level was used to define abnormal vitamin D status as deficiency (<20 ng/ml), insufficiency (20–29 ng/ml), sufficiency (30–80 ng/ml), and toxicity (>80 ng/ml). This study was considered exempt by the Institutional Review Board as all information was de-identified prior to statistical review.

Data were analyzed using STATA 9.2 (College Station, TX), and the *P*-value <0.05 was considered statistically significant. Paired *t*-test was performed to evaluate the efficacy of high-dose intermittent vitamin D supplementation, and other differences by diagnostic category in continuous variables. Chi-squared test was used to describe differences in the prevalence of vitamin D deficiency by gender, race, diagnostic category, and transfusion status.

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