Treatment of vitamin D deficiency in transfusion-dependent thalassemia

Ellen B. Fung,* Catherine Aguilar, Ida Micaily, Drucilla Haines and Ashutosh Lal

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 D2 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 D2, 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 D2 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. Thirty-two transfusion-dependent patients with 25-OH D levels were insufficient 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 38.8 ± 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 D2 supplementation for a total of 66 unique supplementation periods. These patients received a mean of 5 (1–15) doses of 50,000 IU vitamin D2 over 129 (14–521) days. The mean daily dose of vitamin D2 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 D2 increased serum 25-OH D level 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 pg/ml (P < 0.001). The rate of decline was on 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)

<table>
<thead>
<tr>
<th>Type of thalassemia</th>
<th>Gender</th>
<th>Ethnic group</th>
<th>Mean Parathyroid hormone (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Î or Î.E thalassemia</td>
<td>Female</td>
<td>Asian</td>
<td>23.9 (range: 5–68)</td>
</tr>
<tr>
<td>Î or Î.E thalassemia</td>
<td>Male</td>
<td>Caucasian</td>
<td>23.9 (range: 5–68)</td>
</tr>
<tr>
<td>Other/mixed</td>
<td></td>
<td>Other</td>
<td>23.9 (range: 5–68)</td>
</tr>
<tr>
<td>Total</td>
<td>61 (63.5%)</td>
<td>66 (69%)</td>
<td>23 (24%)</td>
</tr>
<tr>
<td>Mean 25-OH vitamin D (ng/ml)</td>
<td>23.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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Transfusion-independent patients, especially those with Hemoglobin H and Hemoglobin 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 D2 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 D2) 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.

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