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Response to Long-term Vitamin D Therapy for Bone Disease in Children with Sickle Cell Disease

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Abstract

Patients with sickle cell disease(SCD) are at risk for bone fragility from multiple factors including vitamin D deficiency. To date, no studies have evaluated the efficacy and safety of long-term vitamin D therapy for bone disease in children with SCD. We report a cohort of four children with SCD found to have severe vitamin D deficiency, secondary hyperparathyroidism, and abnormal bone mineral density treated with monthly high-dose oral cholecalciferol over two years. All patients exhibited a positive response to therapy without hypervitaminosis D or hypercalcemia. Further studies are needed to standardize guidelines for optimal vitamin D dosing and prevention of toxicity.

Keywords

Sickle Cell Anemia; Bone Density; Secondary Hyperparathyroidism; Pediatrics; Vitamin D Deficiency

INTRODUCTION

Patients with sickle cell disease (SCD) are at increased risk for bone disease, such as avascular necrosis, vertebral bone deformities, chronic bone pain, and osteomyelitis [1]. An increased prevalence of vitamin D deficiency and decreased bone mineral density (BMD)

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Contributor's Statement:

Kristen M Williams: Dr. Williams conceptualized and designed the study, coordinated and supervised data collection, wrote the manuscript, and approved the manuscript as submitted.

Margaret T Lee: Dr. Lee coordinated and supervised data collection, critically reviewed and revised the manuscript, and approved the manuscript as submitted.

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Ilene Fennoy: Dr. Fennoy conceptualized and designed the study, coordinated and supervised data collection, critically reviewed the manuscript, approved the manuscript as submitted.

have been reported in both adults and children with SCD [2–4]. Although the exact mechanism of low BMD in SCD is unclear, studies in children with SCD suggest that inadequate vitamin D and calcium might contribute to poor bone mineralization in SCD, and therefore correction of these deficits may improve BMD [2]. Despite the high prevalence of vitamin D deficiency and bone disease, there are no standardized guidelines that outline vitamin D therapy in patients with SCD, particularly with respect to dose efficacy and safety [5].

MATERIALS AND METHODS

As part of a Phase 2 randomized clinical trial of oral vitamin D3 (cholecalciferol) to prevent respiratory complications in pediatric patients with SCD, four of 70 (5.7%) study participants were found at screening to be severely vitamin D deficient (serum 25-hydroxyvitamin D [25(OH)D] levels <5ng/mL) and were not eligible for randomization. Per study protocol, these participants were referred to a pediatric endocrinologist for further clinical evaluation and management, but also continued participation in the open-label arm receiving study drug and laboratory safety measures. Patients received 100,000 IU of oral vitamin D3 every other week for 8 weeks followed by a once monthly dose of 100,000 IU for the remaining 22 months, under observed administration by a research nurse at each study visit. The dosing regimen was designed to achieve a goal of 25(OH)D greater than 30ng/mL. Serum albumin-corrected calcium and spot urinary calcium-creatinine ratios were performed monthly for the first six months, every other month for the following six months, and every three months for the second year to monitor hypercalcemia and hypercalciuria. Patients were evaluated and followed clinically by one of the authors (IF) throughout the duration of the study and thereafter. Serum 25(OH)D and 1,25-dihydroxyvitamin D were measured every one to two months for the first 12 months and then every two to three months for the remainder of the study. Bone markers including parathyroid hormone (PTH), osteocalcin (a marker of bone formation) and c-telopeptide of type 1 collagen (a marker of bone resorption) were assessed at baseline, after 2 months of therapy, and then at 12 months and 24 months on treatment (see Tables 1 for reference values). BMD at four sites (spine, femoral neck, hip, and forearm) via dual-energy x-ray absorptiometry (DXA) was assessed at the start of the study and after 12 months on treatment. BMD was adjusted for height in all patients and a change between initial and follow-up BMD results was considered statistically significant at the 95% confidence interval based on the calculated least significant change [6]. At conclusion of the study, the patients were prescribed daily 600 IU of oral vitamin D.

CASES

Patient 1, a 16 year old African American female with hemoglobin SS (HbSS) and asthma, has a history of multiple fractures with chronic arthritis noted on imaging. She had delayed puberty (menarche 15 years). Upon initial screening, she had a low 25(OH)D level of 4 ng/mL, an elevated intact PTH of 101 pg/mL, and normal serum calcium, osteocalcin, and c-telopeptide levels for age and pubertal status (see Table 1). Baseline DXA showed decreased density at the spine only (see Table 2). With vitamin D supplementation described above, serum 25(OH)D level improved (peak of 40ng/mL) by the second month of therapy and

PTH normalized (31pg/mL) without hypercalcemia or elevated urinary calcium excretion. On repeat DXA 19 months later, there was significant increase in BMD of the forearm without substantial change in the spine or hip. There were no fractures reported during the study period. Two months after completion of the study, the repeat 25(OH)D level decreased to 21 ng/mL.

Patient 2, an 11 year 11 month old Dominican-American female with HbSS and normal pubertal progression (menarche at age 13 years), had no known prior fractures but had evidence of 15% vertebral body depression on spinal x-rays that was insufficient to meet criteria for vertebral compression fracture [7]. At her baseline visit, 25(OH)D level was 4ng/mL and PTH was elevated at 118pg/mL with normal calcium. She did not meet criteria for low BMD on DXA (defined by a z-score <-2.0) [7]. Osteocalcin levels were normal and c-telopeptide levels were elevated as expected with pubertal growth. Serum 25(OH)D levels normalized in the first three months (peak of 66ng/mL at 12 months), with a subsequent decrease in PTH (64pg/mL). She did not have hypercalcemia or increased urinary calcium excretion during the study.

Patient 3, a 14 year 9 month old African American female with HbSS with alpha-thalassemia trait and normal puberty (menarche at 13 years), had a screening hip x-ray concerning for bony infarct of the sacro-iliac joint, but no history of fractures. Her initial 25-(OH)D level was 2.8ng/mL with an elevated PTH of 203pg/mL and normal calcium and bone turnover markers. Her baseline DXA was significant for Z-scores at the spine and hip of -3.3 and -3.6, respectively. Serum 25(OH)D level improved to 42ng/mL by the third month of therapy with appropriate decline in her PTH to 31 pg/mL. Serum calcium levels and urinary calcium excretion were normal. Although the DXA remained abnormal 15 months after start of therapy, there was significant improvement in BMD at her spine and positive trend towards increased density at the hip.

Patient 4, a 14 year 5 month old African-American male with HbSS and normal pubertal history (by report and testicular exam) had documented vertebral body end-plate depressions of the thoracic spine. His baseline laboratory evaluation included a 25(OH)D level of 3.5ng/mL, a PTH level of 78 pg/mL, and normal calcium and osteocalcin levels. C-telopeptide levels were consistent with pubertal growth and initial DXA was within normal limits for age. His peak 25(OH)D level was 46 ng/mL after two months with normalization of PTH and no evidence of vitamin D toxicity. A repeat DXA showed a 16.2% improvement (BMD z-score increasing from -0.4 to 0) at the spine after 15 months. Two months after completion of the study, his 25(OH)D level declined from 34 ng/mL to 19 ng/mL.

DISCUSSION

We described four children with SCD found to have severe vitamin D deficiency, secondary hyperparathyroidism and decreased bone mineralization, treated with oral vitamin D3 100,000 IU every other week for 8 weeks followed by 100,000 IU once per month for the remaining 22 months. This treatment regimen led to correction of vitamin D deficiency, normalization of PTH and improvement in BMD scores, without causing adverse events (toxic levels of 25(OH)D or hypercalcemia).

Lower 25(OH)D levels have been documented in patients with SCD compared to healthy controls even after accounting for race and seasonal change [8–11]. There is limited data on the association of clinical variables with lower vitamin D. Arlet et al, in a study of bone health in sickle cell disease, demonstrated a lack of correlation with sex, type of sickle cell disease or severity [4], while others have shown an inverse relationship of vitamin D levels with age [2, 11]. The relationship of vitamin D status with other non-skeletal clinical manifestations has been evaluated in children with SCD, including the association between low vitamin D and acute vaso-occlusive complications and pulmonary function [12, 13]. In a randomized placebo-controlled trial of a 6-week course of high-dose vitamin D therapy for chronic pain in 39 children and adolescents with SCD, Osunkwo et al demonstrated that high-dose vitamin D was associated with higher 25(OH)D level, fewer numbers of days per week of reported pain, and higher physical activity quality-of-life scores. The high doses (240,000 to 600,000 IU) given over 6 weeks in this pilot study were shown to be safe and required to restore the vitamin D status [14]. However, this clinical trial did not evaluate BMD before and after treatment, but further supported the need for larger, long term supervised high dose vitamin D studies.

Vitamin D deficiency has also been associated with significant increased mean PTH levels in the sickle cell population, and thought to contribute to low BMD [2, 8]. Secondary hyperparathyroidism resulting from chronic vitamin D deficiency can lead to decreased bone mineralization and potentially fracture. An increased risk of nutritional deficiencies from poor calcium intake or malabsorption, decreased weight bearing activities, and possible delayed bone maturation secondary to hypogonadism [2, 10] may further contribute to bone disease in patients with SCD [1]. In a study investigating vitamin D deficiency and bone fragility in adult patients with SCD, Arlet and colleagues found that vitamin D deficiency, defined as 25(OH)D < 6ng/mL, was associated with hyperparathyroidism, increases in bone resorption markers, and fracture [4]. Metabolic changes accompanying severe vitamin D deficiency potentially may worsen or contribute to bone disease. In the pediatric population with SCD, low BMD, as defined by a z-score < -2.0, has been reported in 28–64% of patients [2,3]. Many of the subjects in these studies were found to be vitamin D deficient (<12ng/mL) [3,4,11]. The absence of fracture history in our patients, despite the low bone density, may not only be due to the limited number of cases identified but also to the fact that SCD, unlike thalassemia, has a much lower fracture rate [15].

Some studies propose correction of vitamin D and calcium deficiencies as a strategy to improve bone mineralization and prevent bone disease in patients with SCD. Bisphosphonate therapy is not currently recommended as treatment of bone disease in SCD as some reports point to low bone formation rather than high resorption as the mechanism of decreased bone mineralization in SCD [3,16]. However, a recent study in murine models demonstrated that sickle cell bone disease is associated with osteoblast impairment combined with increased osteoclast activity, further enhanced during recurrent hypoxia/oxygenation stress such as in acute vaso-occlusive crises. Zoledronic acid prevented bone loss by inhibiting osteoclast activity and promoting osteogenic lineage [17], prompting current ongoing clinical trials to assess the effect of bisphosphonates in patients with SCD [18].

Treatment of vitamin D deficiency for bone disease in SCD is not well studied. Adewoye and colleagues treated 14 adults with SCD and vitamin D deficiency with calcium carbonate 1,000 mg daily and vitamin D2 (ergocalciferol) 50,000 IU weekly for 8 weeks then biweekly over a one-year period. Treatment resulted in adequate mean vitamin D levels as well as a 3–6% improvement in BMD [16]. No adverse effects were documented in this group. To date, only one randomized controlled trial has been reported to assess efficacy and safety of vitamin D for treatment of chronic pain in patients with SCD, however, a limited sample size and shorter treatment period reinforces the need for larger studies to help establish consistent treatment guidelines [5]. No long-term vitamin D therapy relating to bone mineralization has been reported in the pediatric sickle cell population. In our small cohort receiving high-dose monthly bolus doses of oral vitamin D3 for 24 months, all patients had 25(OH)D levels that normalized along with improvement in PTH levels secondary to the sustained rise in vitamin D. In two patients, vitamin D levels decreased below 30ng/mL within 2 months of completion of the study while on unobserved recommended doses of 600 IU daily, reinforcing the need for continued maintenance treatment. No patient had evidence of vitamin D toxicity under this directly observed monthly therapy, indicating that long-term supplementation of approximately 100,000 IU monthly dose of cholecalciferol in adolescent patients with SCD is a safe, more convenient and easily observable therapy that is dose equivalent to the Health and Medicine's recommended dose range of 1000–4000 IU per day [19, 20].

Limitations in this case series include a small patient cohort along with lack of standardization in follow-up with respect to laboratory evaluation and timing of bone density analysis. Strengths of this report are that the patients received directly observed therapy over two years with frequent monitoring for adverse effects, further supporting a potential relationship between change in vitamin D status and bone mineral density.

CONCLUSION

These cases illustrate the safety and efficacy of convenient, prolonged monthly high-dose vitamin D therapy in pediatric patients with SCD with improvement in vitamin D status and bone mineralization. Additionally, this report highlights the importance of evaluating vitamin D levels and BMD in an already at risk population, particularly starting with younger patients, in efforts to prevent worsening bone fragility with age. Further studies in a larger cohort of pediatric patients with SCD are needed to formulate standardized guidelines for optimal dosing.

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Abbreviations

25-(OH)D 25 hydroxy-vitamin D

BMD Bone mineral density

DXA	Dual-energy x-ray absorptiometry
HbSS	Hemoglobin SS
PTH	Parathyroid hormone
SCD	Sickle cell disease

References

1. Osunkwo I. An update on the recent literature on sickle cell bone disease. *Curr Opin Endocrinol Diabetes Obes.* 2013; 20(6):539–546. [PubMed: 24150191]
2. Lal A, Fung EB, Pakbaz Z, et al. Bone mineral density in children with sickle cell anemia. *Pediatr Blood Cancer.* 2006; 47(7):901–906. [PubMed: 16317761]
3. Chapelon E, Garabedian M, Brousse V, et al. Osteopenia and vitamin D deficiency in children with sickle cell disease. *Eur J Haematol.* 2009; 83(6):572–578. [PubMed: 19682065]
4. Arlet JB, Courbebaisse M, Chatellier G, et al. Relationship between vitamin D deficiency and bone fragility in sickle cell disease: a cohort study of 56 adults. *Bone.* 2013; 52(1):206–211. [PubMed: 23072921]
5. Soe HHK, Abasa AB, Than NN, et al. Vitamin D supplementation for sickle cell disease. *Cochrane Database of Syst Rev.* 2017; 1:CD010858. [PubMed: 28105733]
6. Baim S, Wilson CR, Lewiecki EM, et al. Precision Assessment and Radiation Safety for Dual-energy X-ray Absorptiometry (DXA): White Paper of the International Society for Clinical Densitometry. *J Clin Densitom.* 2005; 8(4):371–378. [PubMed: 16311420]
7. Crabtree NJ, Arabi A, Bachrach LK, et al. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. *J Clin Densitom.* 2014; 17:225–242. [PubMed: 24690232]
8. Buison AM, Kawchak DA, Schall J, et al. Low vitamin D status in children with sickle cell disease. *J Pediatr.* 2004; 145(5):622–627. [PubMed: 15520761]
9. Kumar J, Muntner P, Kaskel FJ, et al. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. *Pediatrics.* 2009; 124(3):e362–370. [PubMed: 19661054]
10. Kaza PL, Moulton T. Severe vitamin D deficiency in a patient with sickle cell disease: a case study with literature review. *J Pediatr Hematol Oncol.* 2014; 36(4):293–296. [PubMed: 24276034]
11. Rovner AJ, Stallings VA, Kawchak DA, et al. High risk of vitamin D deficiency in children with sickle cell disease. *J Am Diet Assoc.* 2008; 108(9):1512–1516. [PubMed: 18755325]
12. Jackson TC, Krauss MJ, Debaun MR, et al. Vitamin-D deficiency and comorbidities in children with sickle cell anemia. *J Pediatr Hematol Oncol.* 2012; 29(3):261–266.
13. Lee MT, Licursi M, McMahon DJ. Vitamin D deficiency and acute vaso-occlusive complications in children with sickle cell disease. *Pediatr Blood Cancer.* 2015; 62:643–647. [PubMed: 25641631]
14. Osunkwo I, Ziegler TR, Alvarez J, et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. *Br J Haematol.* 2012; 159(2):211–215.
15. Fung EB, Harmatz PR, Milet M, et al. Fracture prevalence and relationship to endocrinopathy in iron overloaded patients with sickle cell disease and thalassemia. *Bone.* 2008; 43(1):162–168. [PubMed: 18430624]
16. Adewoye AH, Chen TC, Ma Q, et al. Sickle cell bone disease: response to vitamin D and calcium. *Am J Hematol.* 2008; 83(4):271–274. [PubMed: 17924548]
17. Dalle CL, Matte A, Valenti MT, et al. Hypoxia-reperfusion affects osteogenic lineage and promotes sickle cell bone disease. *Blood.* 2015; 126(20):2320–2328. [PubMed: 26330244]
18. Vitamin D supplementation and anti-resorptive therapy (bisphosphonates) treatment of young adult patients with sickle cell disease. *Clinicaltrials.gov.* ID NCT02972138.

19. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab.* 2011; 96(1):53–58. [PubMed: 21118827]
20. Ross AC, Manson JE, Abrams SA, et al. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. *J Am Diet Assoc.* 2011; 111(4):524–527. [PubMed: 21443983]

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TABLE 1
Patient Characteristics with Laboratory and Radiological Evaluation at Baseline (T₀) and Three Months (T₃)

Patient ID	Age at Initial Study Visit/Se x	SCD type	Medications	Bone Disease	Vitamin D 25 (ng/mL)		Vitamin D 1,25 (pg/mL)		PTH (pg/mL)		Calcium (mg/dL)		Phosphorous (mg/dL)		Osteocalcin (ng/mL)		C-telopeptide (pg/mL)	
					T ₀	T ₃	T ₀	T ₃	T ₀	T ₃	T ₀	T ₃	T ₀	T ₃	T ₀	T ₃	T ₀	T ₃
1	16y0m Female	HbSS	Hydroxyurea Folic Acid Penicillin VK Flovent	Chronic arthritis of wrist; non- displaced fracture at left phalanx and right metatarsal	4	28	48	37	101	49	8.7	8.8	5.3	5.7	9.1	5.2	364	--
2	11y11m Female	HbSS	Hydroxyurea Folic Acid Penicillin VK	Central end plate depression of thoracic vertebral bodies	4	49	45	77	118	77	9.2	9.1	4.6	--	42.6	89.5	753	608
3	14y9m Female	HbSS with alpha thalassemia trait	Hydroxyurea Folic Acid Penicillin VK	Sacroiliac Joint bony infarct	2.8	42	--	118	203	52	9.2	9.8	4.2	4.8	23.3	31.9	542	603
4	14y5m Male	HbSS	Hydroxyurea Folic Acid Penicillin VK	Mid plate irregularities of thoracic vertebrae; central end plate depression of lumbar vertebral bodies	3.5	46	94	98	78	72	9.1	9.1	4.1	4.5	14.2	26.3	673	1588

Normal values: Vitamin D 25 30–100ng/mL; Vitamin D 1,25 21–65 pg/mL; parathyroid hormone (PTH) 10–65 pg/mL; serum calcium 8.7–10.2 mg/dL; serum phosphorous

2.7–4.5 mg/dL; osteocalcin (Esoterix, Inc, Austin TX) 37–154 ng/mL, 10–11 years, 42–225 ng/mL, 12+ years; C-telopeptide (LabCorp, Burlington NC) 115–748 pg/mL, male,

112–738 pg/mL, female

TABLE 2
Bone Mineral Density by Dual-energy X-ray Absorptiometry at Baseline and Follow-up

Patient	Baseline z-score	Follow-up z-score	% Change
1	AP spine -2.0	AP spine -2.2	1.5%
	Femoral Neck -0.6	Femoral Neck -1.2	--
	Total Hip -0.3	Total Hip -0.4	1.6%
	Forearm 0.1	Forearm 1.2	10.1% (*)
2	AP spine -1.3	AP spine -1.3	0%
	Femoral neck -1.1	Whole Body -0.9	
	Total Hip -0.5		
	Forearm -1.2		
3	AP spine -3.3	AP spine -2.1	13.7% (*)
	Femoral Neck -3.3	Femoral Neck -2.5	--
	Total Hip -3.6	Total Hip -2.4	2.9%
	Forearm -1.8	Forearm -1.0	5.3%
4	AP spine -0.4	AP spine 0.0	16.2% (*)
	Femoral Neck -0.5	Whole Body 0.9	
	Total Hip -0.4		
	Forearm 1.0		

Low bone mineral density is defined by a z-score less than -2.0 SD

* Statistically significant change at 95% confidence level