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Vitamin-D Deficiency and Comorbidities in Children with Sickle Cell Anemia

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Abstract

Vitamin-D deficiency is known to be common among patients with Sickle Cell Anemia (SCA). Vitamin-D levels were measured in 139 children (aged 7.9-15.1 years) to study its association with SCA morbidities; severe deficiency (<10 ng/mL) was present in 64.0% and only 2.2% were sufficient (>30 ng/mL). Vitamin-D levels were associated with pulmonary function (FEV1), but not associated with either rates of acute pain or acute chest syndrome episodes. Further studies are needed to be able to compare outcomes in those with deficiency to those with sufficiency, as well as to treating patients with SCA with vitamin-D to better establish a possible link, if any, between vitamin-D and SCA morbidity.

Keywords

Vitamin-D; sickle cell anemia; acute chest syndrome; pain crisis; asthma

Introduction

The national prevalence of vitamin-D deficiency (≤20 ng/mL) in all children is 14% and in non-Hispanic black adolescents is 50%[1]. Children with Sickle Cell Anemia (SCA) are 5.3 times more likely to develop vitamin-D deficiency than healthy African-American controls[2]; and it is estimated that 65% of children with SCA had severe vitamin-D deficiency (≤10 ng/mL)[3], possibly due to increased skin pigmentation, reduced exposure to sunlight, and less intake of vitamin-D[4,5]. Despite these findings, vitamin-D levels are not routinely checked or treated in patients with SCA. Since vitamin-D deficiency is related

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Ethical consent was obtained for all subjects of this study per the Human Research Protection Office of Washington University.

Declaration of Interest Statement

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to increased asthma symptoms and chronic pain in the general population[6-11], we tested the hypothesis that low levels of vitamin-D would be associated with comorbidities in SCA.

Materials and Methods

We conducted a cross-sectional study in 139 pediatric patients with SCA to examine vitamin-D deficiency, asthma, and SCA morbidity. The study was approved by the Washington University School of Medicine Human Research Protection Office and performed after subjects signed an informed consent. These subjects are part of the Sleep and Asthma Cohort Study (SAC) which is a four-year multi-center observational cohort study of patients with SCA, primarily looking at the effect of asthma severity on SCA morbidity. This study involved two sites in the United States (Cleveland, Ohio and St. Louis, Missouri) and one in London, England. All patients in the SAC study who had measured vitamin-D levels were included. Children on chronic transfusion were excluded from the SAC study. Children who were treated with hydroxyurea were excluded from this study. Participants underwent an evaluation for asthma including spirometry, total serum IgE, allergy skin testing, peripheral blood eosinophil count, vitamin-D level measurements, and retrospective chart review of ACS and pain episodes for the previous 3 years. 25-hydroxyvitamin-D levels were determined by direct, competitive chemiluminescence immunoassay (CLIA) using the DiaSorin LIAISON platform. Seasonal variation of vitamin-D levels was assessed by month.

Differences of vitamin-D levels by gender, study site, and season were assessed using the Wilcoxon Mann-Whitney test (gender and study site) and Kruskal Wallis (season). Relationships between patient demographic and clinical characteristics, including vitamin-D level, with number of pain episodes and number of ACS episodes were assessed using negative binomial regression. Associations between the patient characteristics and levels of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1 to FVC as % predicted using equations from Wang et al.[12] for African American children and the presence of asthma either by parent report of a doctor diagnosis or use of an asthma medication were assessed using OLS regression and logistic regression, respectively. Multivariable models predicting each outcome of interest were first constructed including all potential covariates: Vitamin-D, age, gender, body mass index percentile, white blood cell count, hemoglobin and immunoglobulin E (for asthma and lung function models only). A second reduced model for each outcome of interest was then constructed including all nominally significant predictors ($P<0.20$) from the full model. As an alternative to analyzing vitamin-D levels as a continuous variable, we also analyzed severe vitamin-D deficiency (levels <10 mg/dL vs. 10-30 mg/dL). All analyses were performed using SAS v 9.2 (SAS Institute, Inc., Cary, NC). Estimates of associations are presented with 95% confidence intervals. Two tailed *P* values of less than 0.05 were considered to be significant.

Results

The median age of the population was 11.5 years (inter-quartile range [IQR] 7.9 – 15.1) and 52.5% were male. Median hemoglobin was 8.1 (IQR 7.2 – 8.9); twenty-four percent of the patients had two or more pain episodes over the previous three years and thirteen percent had two or more episodes over the previous three years. Among the cohort, 96.4% had vitamin-D deficiency (≤20 ng/mL), of these 64.0% had severe deficiency (<10 ng/mL); 1.4% were insufficient (20.01-29.9), and only three subjects, 2.2% had sufficient levels (≥30 ng/mL), with an overall median of 7.9 ng/mL (IQR 4.9 – 11.8) (Table 1). Although deficient year round, vitamin-D levels had a seasonal variation ($\chi^2=20.3$, df 3, $p<0.001$), with highest levels in the summer at 10.7 ng/mL (IQR 8.6 – 13.4) and lowest in the winter at 5.4 ng/mL (IQR 3.9 – 8.2). There was no relationship between vitamin-D levels and latitude between

London, UK; Cleveland, OH; and St. Louis, MO (χ^2=0.156, p=0.925). Vitamin-D levels were lower in older patients (ρ= −.46; 95% confidence interval [CI]: −0.58, −0.32; p<0.001) and lower for females (male median 8.6 ng/mL, IQR 5.9 – 13.1; female median 7.5 ng/mL, IQR 4.4 – 10.6; p=0.038). Vitamin-D levels were not significantly correlated with BMI percentile (ρ=0.00; CI: −0.17, 0.17; p=1.00) or BMI Z-score (ρ=0.05; CI: −0.12, 0.21; p=0.593). These relationships with age, gender, and season were also present in the bivariate analysis of patients with severe deficiency (levels <10 mg/dL vs. levels ≥10 mg/dL).

Vitamin-D trended towards significance in the full model for FEV_1 % predicted, and in the reduced model (with predictors p<0.20) reached significance (Table 2). This association was also found in a reduced model when using severe vitamin-D deficiency as a predictor rather than continuous vitamin-D levels (reduced model results: severe vitamin-D deficiency β= −5.59, 95% CI −10.45 to −0.72, p=0.025; white blood cell count β= −0.17, 95% CI −0.38 to 0.05, p=0.129).

In full multivariable models, vitamin-D was not associated with number of pain (β=0.01, 95% CI −0.06 to 0.07, p=0.813) or ACS episodes (β=0.01, 95% CI −0.08 to 0.09, p=0.878), asthma diagnosis (OR 1.01, 95% CI 0.93 – 1.09, p=0.881), FVC % predicted (β=0.38, 95% CI −0.20 to 0.96, p=0.194), or FEV_1/FVC % predicted (β=0.04, 95% CI −0.28 to 0.36, p=0.800). Reduced models for these outcomes (with predictors p<0.20 from full models) were as follows: for number of pain episodes: age β=0.12, 95% CI 0.05 to 0.20 (p=0.002); for number of ACS: BMI percentile β= −1.33, 95% CI −2.62 to −0.04 (p=0.043), and hemoglobin β= −0.44, 95% CI −0.78 to −0.10 (p=0.011); for asthma: BMI percentile OR=3.40, 95% CI 0.98 to 11.82 (p=0.054) and hemoglobin OR=0.77, 95% CI 0.57 – 1.06 (p=.114); for FVC% predicted: vitamin-D β=0.31, 95% CI 0.21 to 0.83 (p=0.239), IgE β=0.006, 95% CI −0.002 to 0.014 (p=0.036) and BMI percentile β=10.4, 95% CI 1.4 to 19.3 (p=0.024); for FEV_1/FVC % predicted: age β= −0.78, 95% CI −1.11 to −0.44 (p<0.001) and hemoglobin β=0.95, 95% CI −0.28 to 2.18 (p=0.130). Severe vitamin-D deficiency (levels <10 mg/dL) was not significantly associated with pain episodes, ACS episodes, asthma, FVC or FEV/FVC as compared to patients with levels ≥10 mg/dL.

Discussion

This study emphasizes the high prevalence of severe vitamin-D deficiency among patients with SCA across different centers and latitudes, which suggests that cultural, behavioral and environmental factors play a major role more than latitude in the degree of this deficiency in this population[13]. We found that 96.4 % of the patients had values below 20 ng/mL, which by the Institute of Medicine has been considered a level that confers increased risk for osteomalacia in the general population of adolescents and young adults[14]. Small sample studies in adults and children with SCA confirm the associations between low vitamin-D and lumbosacral and femoral osteomalacia and increased bone fragility[15,16]. Moreover, vitamin-D supplementation for 12 months in 14 young adults with SCA and osteomalacia increased their mean 25(OH) vitamin-D levels to 34 ng/mL and significantly improve their lumbosacral and femoral BMD despite a lack of change in their PTH levels, suggesting that early screening for vitamin-D deficiency is required to prevent their bone mineral complications[16]. Also, this population seems to have lost the bone resistance to PTH actions seen in African Americans, thus bigger interventional trials should be performed to establish if early treatment with vitamin-D is required[17].

This is the first study to evaluate the association between vitamin-D status and acute pain episodes and ACS in children with SCA. In contrast to a previous study by Osunkwo reporting association between persistent chronic pain and lower vitamin-D levels, we did not find any relationship between vitamin-D levels and the number of acute pain episodes, ACS

episodes when controlling for age, season, BMI, hemoglobin, white blood cells, and oxygen saturation. It is possible that we failed to see an impact on clinical outcomes because the levels of vitamin-D were so uniformly low in these patients that we were unable to tell what effect vitamin-D deficiency, insufficiency, or sufficiency would have on the clinical outcomes studied.

In children, previous studies suggest that those with SCA have significantly lower FEV_1 and FVC than controls matched for sex, race and height, but similar FEV_1/FVC[18,19]. These differences were more marked in older children[18]. In this study vitamin-D deficiency was significantly associated with increasing in age but more important is that we found an association between vitamin-D and pulmonary function, particularly FEV_1, and severe vitamin-D deficiency (≤10 mg/mL) was a predictor for lower FEV_1. Since asthma is a common comorbidity in SCA with a reported prevalence of 30-70%[20], our finding highlights the importance of the extra skeletal effects of vitamin-D, and suggest that early replacement of vitamin-D is ideal given the low risk of toxicity with its supplementation.

There are limitations present in our study. This study cohort is a sample of children with SCA that were selected from children attending sickle cell disease clinics at three centers and they do not represent all children with SCA. However, we believe that the broad entry criteria and multi-institution study design achieved a non-biased, representative sample. Limitations to our study include that the assessment of pain crisis and ACS is retrospective to only 3 years. Furthermore, the rate of pain crisis and ACS was calculated three years before the vitamin-D level with the assumption that the vitamin-D level was low three years ago or persistently low. Although we excluded those patients on hydroxyurea therapy, vitamin-D has not been found to be related to hydroxyurea use by other authors[13]. Another limitation of our study is that we do not have food diaries and intake of possible nutritional supplements taken by these subjects, but regardless if some of the patients were on any possible vitamin supplement, given the degree of deficiency, it is likely that it wasn't sufficient to achieve adequate replacement.

The severity of vitamin-D deficiency shown in this cohort, the differences in lung function and the evidence of bone mineral density improvement with vitamin-D in this population may warrant close monitoring of vitamin-D levels and replacement as standard of care for pediatric children with SCA. An interventional study or a case control study of patients with SCA and various degrees of vitamin-D deficiency and sufficiency are needed, to determine the ideal vitamin-D levels required for this population that is related to better clinical outcomes.

Conclusion

Patients with Sickle Cell Anemia have increased risk of vitamin-D deficiency. In this study cohort, vitamin-D deficiency was related to decreased pulmonary function but not to acute sickle cell morbidity. More research is needed to evaluate the effects of this deficiency on morbidity in patients with SCA, especially regarding bone health.

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References

1. Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial us adolescent population: the National Health and Nutrition Examination Survey III. Pediatrics. 2009; 123:797–803. [PubMed: 19255005]
2. Rovner AJ, Stallings VA, Kawchak DA, Schall JI, Ohene-Frempong K, Zemel BS. High risk of vitamin D deficiency in children with sickle cell disease. J Am Diet Assoc. 2008; 108:1512–1516. [PubMed: 18755325]
3. Buison AM, Kawchak DA, Schall J, Ohene-Frempong K, Stallings VA, Zemel BS. Low vitamin D status in children with sickle cell disease. J Pediatr. 2004; 145:622–627. [PubMed: 15520761]
4. Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. Am J Clin Nutr. 2007; 86:150–158. [PubMed: 17616775]
5. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266–281. [PubMed: 17634462]
6. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol. 2007; 120:1031–1035. [PubMed: 17919705]
7. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin d and pulmonary function in the third national health and nutrition examination survey. Chest. 2005; 128:3792–3798. [PubMed: 16354847]
8. Brehm JM, Celedon JC, Soto-Quiros ME, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. Am J Respir Crit Care Med. 2009; 179:765–771. [PubMed: 19179486]
9. Brohult J, Jonson B. Effects of large doses of calciferol on patients with rheumatoid arthritis. A double-blind clinical trial. Scand J Rheumatol. 1973; 2:173–176. [PubMed: 4129296]
10. McBeth J, Pye SR, O'Neill TW, et al. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. Ann Rheum Dis. 2010; 69:1448–1452. [PubMed: 20498201]
11. Hollams EM, Hart PH, Holt BJ, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. Eur Respir J. 2011; 38:1320–1327. [PubMed: 21565922]
12. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol. 1993; 15:75–88. [PubMed: 8474788]
13. Goodman BM 3rd, Artz N, Radford B, Chen IA. Prevalence of vitamin D deficiency in adults with sickle cell disease. J Natl Med Assoc. 2010; 102:332–335. [PubMed: 20437740]
14. Ross, AC.; Taylor, CL.; Yaktine, AL.; Del Valle, HB. Dietary Reference Intakes for Calcium and Vitamin D. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Institute of Medicine. Food and Nutrition Board. , editor. The National Academies Press; Washington, DC: 2011. p. 6-7.
15. Adewoye AH, Chen TC, Ma Q, et al. Sickle cell bone disease: response to vitamin D and calcium. Am J Hematol. 2008; 83:271–274. [PubMed: 17924548]
16. Osunkwo I, Hodgman EI, Cherry K, et al. Vitamin D deficiency and chronic pain in sickle cell disease. Br J Haematol. 2011; 153:538–540. [PubMed: 21275953]
17. Cosman F, Morgan DC, Nieves JW, et al. Resistance to bone resorbing effects of PTH in black women. J Bone Miner Res. 1997; 12:958–966. [PubMed: 9169356]
18. Sylvester KP, Patey RA, Milligan P, et al. Pulmonary function abnormalities in children with sickle cell disease. Thorax. 2004; 59:67–70. [PubMed: 14694252]
19. Pianosi P, D'Souza SJ, Charge TD, Esseltine DE, Coates AL. Pulmonary function abnormalities in childhood sickle cell disease. J Pediatr. 1993; 122:366–371. [PubMed: 8441089]
20. Morris CR. Asthma management: reinventing the wheel in sickle cell disease. Am J Hematol. 2009; 84:234–241. [PubMed: 19229984]

Table I

Descriptive characteristics of the sample of sickle cell patients (N=139)

Variable	*n (%)*
Gender	
Male	73 (52.5)
Female	66 (47.5)
Diagnosed with Asthma	59 (42.5)
	Median (IQR)
Age (years)	11.5 (7.9 – 15.1)
BMI percentile	0.50 (0.25 – 0.75)
25,OH Vitamin D level (ng/mL)	7.9 (4.9 – 11.8)
Hemoglobin, g/dL	8.1 (7.2 – 8.9)
Baseline oxygen saturation	96.7 (94.2 – 98.9)
White blood cell count	11.8 (9.5 – 13.6)
IgE	48.5 (20.6 – 157.0)
Pre FEV_1 %	87.2 (77.1 – 97.1)
Pre FVC %	92.1 (80.2 – 100.5)
Pre FEV_1/FVC %	97.5 (92.5 – 101.9)
Pain Episodes, treated in hospital, past 3 years	0 (0-1)
ACS Episodes, treated in hospital, past 3 years	0 (0-1)

Table II

Regression models for lung function (pre FEV_1 % predicted)

Predictors	Full model		Model with reduced set of covariates (P<0.20 in full model)	
	β(95% CI)	P	β(95% CI)	P
Age	−0.07 (−0.76, 0.63)	.850		
Gender (female vs male)	−0.08 (−5.24, 5.09)	.976		
BMI percentile	5.26 (−3.32, 13.84)	.228		
White blood cell count	−0.20 (−0.46, 0.06)	.129	−0.20 (−0.41, 0.02)	.074
Hemoglobin	1.11 (−1.13, 3.36)	.329		
Vitamin D	0.42 (−0.13, 0.97)	.135	0.49 (0.08, 0.90)	.020
IgE	0.003 (−0.004, 0.010)	.410		