Journal Pre-proof

Vitamin D Supplementation and Pain-Related Emergency Department Visits in Children with Sickle Cell Disease

Anna M. Hood, Charles T. Quinn, Christopher D. King, Lisa M. Shook, James L. Peugh, Lori E. Crosby

PII: S0965-2299(19)30926-4

DOI: https://doi.org/10.1016/j.ctim.2020.102342

Reference: YCTIM 102342

To appear in: *Complementary Therapies in Medicine*

Received Date: 3 July 2019

Revised Date: 14 January 2020

Accepted Date: 10 February 2020

Please cite this article as: Hood AM, Quinn CT, King CD, Shook LM, Peugh JL, Crosby LE, Vitamin D Supplementation and Pain-Related Emergency Department Visits in Children with Sickle Cell Disease, *Complementary Therapies in Medicine* (2020), doi: https://doi.org/10.1016/j.ctim.2020.102342

Vitamin D Supplementation and Pain-Related Emergency Department Visits in Children with Sickle Cell Disease

Anna M. Hood PhD[1], Charles T. Quinn MD, MS[2,3], Christopher D. King PhD[2,4], Lisa M. Shook MA, MCHES[2,3], James L. Peugh PhD[1,2], Lori E. Crosby PsyD[1,2]

[1] Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, London, United Kingdom

[2] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio

[3] Cancer and Blood Diseases Institute, Division of Hematology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[4] Pain Research Center, Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[5] Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

All correspondence concerning this article should be addressed to Anna M. Hood Ph.D., Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health, London, United Kingdom, 30 Guilford Street, London, WC1N 1EH. Telephone: 020.7905.2744, Email: a.hood@ucl.ac.uk.

Abstract

Objectives

Sickle cell disease (SCD) is the most prevalent inherited hematological disorder and affects 100,000 individuals in the United States. Pain is the most common cause of emergency department (ED) visits in the SCD population, which profoundly affects quality of life. Vitamin D supplementation is a potential target for reducing pain. Thus, the goal of the present study was to identify the prevalence of vitamin D deficiency and explore the relationship between vitamin D supplementation and ED visits in pediatric patients with SCD.

Design

We conducted a retrospective chart review of 110 patients with SCD aged 8 to 16 years who had at least one ED visit for SCD pain during the 6-year study period. Patients were categorized into three vitamin D supplementation groups: patients who did not receive supplementation, patients supplemented with 25-hydroxyvitamin D levels (< 30 ng/mL), and patients supplemented with at least one sufficient 25-hydroxyvitamin D level (≥ 30 ng/mL).

Results

Overall, 45% of patients were vitamin D deficient. Only 20% of patients had sufficient vitamin D levels. This number increased to 55% when examining only patients who did not receive vitamin D supplementation. For patients supplemented with vitamin D, the number of ED visits was significantly lower after they reached the sufficient range (≥ 30 ng/mL), $p = .03$.

Conclusions

Our findings indicate that reductions in the number of pain-related ED visits may be achieved by normalizing 25-hydroxyvitamin D levels with supplementation. In addition, findings highlight the need for screening and vitamin D supplementation being incorporated into routine care for pediatric patients with SCD.

Keywords: sickle cell disease; vitamin D deficiency; vitamin D supplementation; pain; emergency department

Introduction

Sickle cell disease (SCD) is the most prevalent inherited hematological disorder and affects 100,000 individuals in the United States.[1] Pain remains the leading cause of morbidity and frequency of pain episodes is associated with higher mortality rates.[2] SCD patients experience both acute and chronic pain with a complex etiology dependent on several factors including somatic tissue injury and bone infarction subsequent to vaso-occlusive events, central sensitization (e.g., nociceptive and neuropathic), and peripheral nerve injury.[3] Vaso-occlusion can be precipitated by external factors including dehydration, infection, cold weather, physical exercise, alcohol, and pregnancy, but is also unpredictable and can occur without warning creating additional challenges for prevention.[4]

Vaso-occlusive pain episodes are the most common cause of emergency department (ED) visits and these episodes profoundly affect quality of life.[5] Current pain management for individuals with SCD is multidimensional, but first line treatment is often pharmacological (e.g., opioids). Nonpharmacological complements to pharmacological therapies include physical (e.g., massage, exercise), psychological (e.g., cognitive behavioral therapy, relaxation, biofeedback, self-hypnosis), and nutritional strategies (e.g. folic acid, vitamins).[6] Gaining a better understanding of the mechanisms underlying SCD pain will be essential to developing future treatment strategies.

Vitamin D has emerged as a public health focus and, in the past decade, has been considered as a potential target for reducing pain in individuals with SCD. Accumulating evidence indicates that vitamin D deficiency is common in children and adults with SCD. Unfortunately, there is currently no uniform classification in the literature; however, serum levels of 25-hydroxy-vitamin D (25-OHD) of $\leq$ 20 ng/mL are generally considered as deficient.[7] In the non-SCD population, the prevalence of vitamin D deficiency for children and adolescents in the United

States is estimated to be 7 – 14%.[8] For non-Hispanic Black children and adolescents, prevalence rates rise to as high as 50%, even after controlling for a number of potential covariates (e.g., obesity, milk intake, television watching, video game and computer use, and vitamin D supplement use), highlighting the decreased ability of Black children to synthesize vitamin D from sunlight.[9] Children with sickle cell anemia (SCA or HbSS) are more than five times more likely to develop vitamin D deficiency than non-SCD Black children.[10]

Reasons posited for the higher prevalence of vitamin D deficiency in the SCD population compared to other Black children include decreased appetite with higher nutritional demands to sustain normal physiologic functioning, hyper-myelination, renal impairment, and reduced amounts of the vitamin D binding protein.[7] In addition to being important in normal bone health and development, vitamin D is thought to influence peripheral and parasympathetic nerve function through anti-inflammatory effects mediated by reduced pro-inflammatory cytokines and prostaglandin release and effects on T-cell responses.[11] Specifically, vitamin D changes the T-cell responses producing higher levels of Th2 and Treg cells instead of producing pro-inflammatory Th1 and Th17 cells.[12] Thus, vitamin D deficiency may lead to alterations in neural and immune processes that contribute to the experience of pain.

There is evidence for a link between vitamin D and non-SCD pain, although large randomized control trials are lacking.[13,14] Only recently has this relationship between examined in the pediatric SCD population. Pilot randomized control trials (RCT) have found that young male children who received daily vitamin D supplements for 6 months prior to undergoing circumcision had four times fewer post-operative pain episodes,[15] and that there was a trend towards fewer pain days between visits for a group treated with vitamin D supplements in a 16-week double-blind pilot RCT.[16]

The majority of investigations assessing vitamin D and pain in children with SCD have occurred outside of the United States. In general, vaso-occlusive episodes[17–23] and hospital admissions[24] occurred less frequently and fewer pain episodes and hospitalizations were associated with higher serum 25-OHD levels. In contrast, two studies conducted in North America have found no significant relationships between lower serum 25-OHD levels and number of acute pain episodes;[25,26] yet, in both of those studies the median number of pain episodes in the samples was low. Further, another study in the United States found that degree of vitamin D insufficiency was not significantly related with the number of hospital admissions, but was related with average length of stay in the hospital.[27] Overall, the small body of research suggests that vitamin D deficiency can impact pain outcomes in patients with SCD.

In the largest-scale study to date of serum 25-OHD levels and SCD, four years of medical records were assessed in 1500 adult patients with SCD. The research team found that SCD patients with severe vitamin D deficiency (<14.1 ng/mL) had on average more than 10 hospital and ED visits per year compared to fewer than 2 visits per year from patients with higher serum 25-OHD levels (>34 ng/mL).[28] Given the findings in adult SCD patients, the goal of the present study is to determine whether a similar relationship between ED visits and vitamin D deficiency were present in a pediatric SCD population.

Using records from patients with SCD between 8 to 16 years of age who had visited the hospital ED at least once between July 2012 and July 2018, and had at least one serum 25-OHD level, our study aimed to: 1) describe the prevalence of vitamin D deficiency in the pediatric SCD population, and 2) explore the relationship between vitamin D supplementation and ED visits. We hypothesized that patients with SCD would have high prevalence of vitamin D deficiency and that

patients who received vitamin D supplementation would have fewer ED visits for SCD-related pain than patients who did not.

Materials and Method

Participants

The study population was a convenience sample of patients followed at our large medical center. More than 75% of the SCD patients live within a 15-mile radius; therefore, almost all ED visits occur at our center. We included patients who had visited the hospital ED at least once for SCD-related pain when they were between 8 to 16 years of age in the 6-year period between July 2012 and July 2018. We did not include patients less than 6 years of age because our data demonstrated that most younger patients with SCD did not have pain-related ED visits. Patients over 16 years of age were excluded as they would have aged out of pediatric services by the end of the study period.

Patients had at least one serum 25-OHD level. All patients with SCD irrespective of genotype (i.e., HbSS, HbSC, and HbSβ^+ or HbSβ^0) were selected for inclusion in this study. Exclusion criteria included identifying as a race other than Black (due to concerns about cultural differences related to the use of the ED for pain as the patients were recent immigrants) and an ED visit for a reason other than SCD-related pain (e.g., thumb fracture). Five participants were excluded for these reasons. Additionally, 17 patients were excluded because they had ED visits but no measured serum 25-OHD levels during the study period. Patients receiving hydroxyurea (HU) therapy and chronic transfusion were not excluded.

Procedures

Beginning in 2012, individualized home pain management plans (HPMP) were incorporated into the care of outpatients aged 5 years to 21 years of age at the Comprehensive Sickle Cell Center at our institution. It is within the context of patients having individualized HPMPs that we examined the relationship between ED visits and vitamin D deficiency. Elements of the HPMP include both pharmacologic and nonpharmacologic pain management strategies with a goal to reduce preventable ED visits and subsequent hospitalizations. The HPMP was successful as 100% of eligible patients who needed an HPMP received one during an outpatient clinic visit and the vast majority met with the team psychology provider. Of particular relevance, following implementation of the intervention, the percentage of ED visits for SCD uncomplicated pain decreased by 84%.[29]

Via a retrospective review of the electronic medical record (EMR), we abstracted clinical (i.e., genotype, ED visits and reasons), demographic (i.e., age, gender, race), and serum 25-OHD levels. The institutional review board of our institution approved the study and granted a waiver of informed consent.

In line with The Endocrine Society's and our institution guidelines, we define vitamin D deficiency as a 25-OHD serum level below 20 ng/ml (50 nmol/L), vitamin D insufficiency as a 25-OHD serum level of 20 – 29.99 ng/mL (52.5 – 74.98 nmol/L), and vitamin D sufficiency as a 25-OHD serum level of ≥ 30 ng/mL (≥ 50 nmol/L).[30] The goal of vitamin D supplementation is to maintain serum 25-OHD levels ≥ 30 ng/mL. Our institutional guidelines specify that 25-OHD levels should be obtained every 6 months to yearly, beginning at 1 year of age. For vitamin D deficiency, 50,000 IU vitamin D3 is given weekly for 16 weeks. If the 25-OHD level is 20-30 ng/mL at the end of 16-week therapy, then patients begin 1,000-2,000 IU daily or 50,000 IU monthly. If the level is >30, the patients begin 400-1000 IU vitamin D3 daily. If 25-OHD levels

are above 100 ng/mL on two consecutive monthly levels, the dose is decreased to maintain the level between 30 and 100ng/mL. Despite these guidelines, not all patients were prescribed vitamin D as part of routine medical care for various reasons (e.g., individual providers concerns, desire to focus on hydroxyurea adherence, patient or family uncertainty, irregular clinic visits).

SCD patients were categorized into three groups. (1) Non-supplemented patients who did not receive *any* vitamin D supplementation during the study period (Group A). (2) Patients supplemented with vitamin D but who *did not* have at least one serum 25-OHD level that was in the sufficient range (≥ 30 ng/mL) during the study period (Group B). (3) Patients supplemented with vitamin D who *did* have at least one serum 25-OHD level that was in the sufficient range (≥ 30 ng/mL) during the study period (Group C). This grouping strategy is in line with previous research that has demonstrated the importance of reaching optimal serum 25-OHD levels to reduce to SCD-related pain.[16]

Statistical Analyses

All analyses were conducted using the R statistical package.[31] Mean serum 25-OHD levels were calculated by averaging all available values for each patient during the study period. These mean serum 25-OHD levels were used to determine if patients were in the deficient, insufficient, or sufficient range. Fisher's Exact Test was used to assess for significant differences in groups based on serum 25-OHD levels (e.g., deficient and insufficient) because some cells had sample sizes of less than 10 patients. Analysis of Variance (ANOVA) analyzed differences in serum 25-OHD levels based on vitamin D status (i.e., supplementation groups A, B, and C). Genotype was examined as a covariate to see if it explained variance in ED visits. Given the difficulty of retrospectively tracking whether patients maintained chronic blood transfusion and adhered to

hydroxyurea therapy throughout the 6-year study period, we did not feel confident that classifications would accurately reflect patients' status and so treatment type or length were not included as covariates in analyses. Effect sizes (partial eta-squared; η^2) were calculated for all effects.

Paired samples t-tests with Cohen's d as the measure of effect size assessed for differences in the number of ED visits before and after supplemented patients achieved sufficiency (e.g., we tested to determine if supplemented patients had more ED visits before they had a serum 25-OHD level that reached the sufficient range (≥ 30 ng/mL) compared to afterwards. We determined statistical significance for all tests at an alpha level of $p < .05$ two-tailed.

Results

Participants

The overall sample of 110 pediatric patients with SCD were on average 11 years of age, 53% male, all identified as African American/Black, and had the majority had the following hemoglobin types: 72% HbSS and 24% HbSC. These demographics were generally similar to our larger SCD clinic population (M=11 years; 48% male; 60% HbSS; 28% HbSC). Patient characteristics are reported in Table 1 separated by vitamin D supplementation status (Groups A, B, and C). All three groups were similar with respect to race, gender, and hemoglobin type, $p > .05$. Non-supplemented patients were significantly younger at their first ED visit than both groups of supplemented patients, $p < .01$. The two groups of vitamin D supplemented patients received supplementation for a similar number of months, $p > .05$.

Vitamin D Deficiency

Our results identified that approximately 45% (n = 48) of patients with SCD were vitamin D deficient (< 20 ng/mL). Only 20% of patients (n = 22) had sufficient vitamin D levels. When patients supplemented with vitamin D were excluded, the prevalence of vitamin D deficiency was 55% (17 of 31 patients). Patients in the deficient range (< 20 ng/mL) had on average 3.58 ED visits during the study period, patients in the insufficient range (20-29.99 ng/mL) had 3.87 ED visits, and patients in the sufficient range (≥ 30 ng/mL) had only 2.67 ED visits. ANOVA analyses demonstrated that patients with the HbSS and sickle-β^0-thalassemia (HbSβ^0) genotypes (likely greater clinical disease severity) had significantly more ED visits than patients with the HbSC and sickle-β^+-thalassemia (HbSβ^+) genotypes (likely less clinical disease severity), $F(2, 106) = 6.02$ $p = .02$. However, there was not a significant difference in number of ED visits between patients in the deficient, insufficient, and sufficient ranges, $F(2, 106) = .98$ $p = .38$.

Vitamin D Supplementation

Since vitamin D supplementation can impact serum 25-OHD levels, we further explored differences in serum 25-OHD levels in SCD patients with and without documented vitamin D supplementation. First, we assessed the percentage of patients with vitamin D deficiency within each group.

Twenty-eight percent of patients in the overall sample (n = 31) were in Group A (non-supplemented patients). Of these non-supplemented patients, 55% (n = 17) had mean serum 25-OHD levels in the deficient range (< 20 ng/ml). Thirty percent of patients (n = 33) were in Group B (supplemented < 30 ng/mL). Of these patients, 73% (n = 24) had mean serum 25-OHD levels in the deficient range. Forty-two percent of patients (n = 47) were in Group C (supplemented ≥ 30 ng/mL). Of these supplemented patients, only 15% (n = 7) had mean serum 25-OHD levels in the

deficient range. Fisher's Exact Test demonstrated that the percentage of patients in the deficient and insufficient range significantly differed by group supplementation status, $p < .0001$ (see Figure 1). There were too few patients in the sufficient range ($n < 5$) to statistically test differences between groups.

Next, we assessed for differences based on mean serum 25-OHD levels between groups. ANOVA analyses revealed a significant overall effect of group status, $F(2, 106) = 13.68$, $p < .0001$, $\eta^2 = .28$. Specifically, there was not a significant main effect of genotype. However, Group A (non-supplemented patients) had significantly lower mean serum 25-OHD levels compared to Group B (supplemented < 30 ng/mL), $t(106) = 2.39$, $p = .02$) and Group C (supplemented ≥ 30 ng/mL), $t(106) = 3.34$, $p = .001$). Additionally, Group C had significantly lower mean serum 25-OHD levels than Group B, $t(106) = 6.00$, $p < .0001$ (see Table 1).

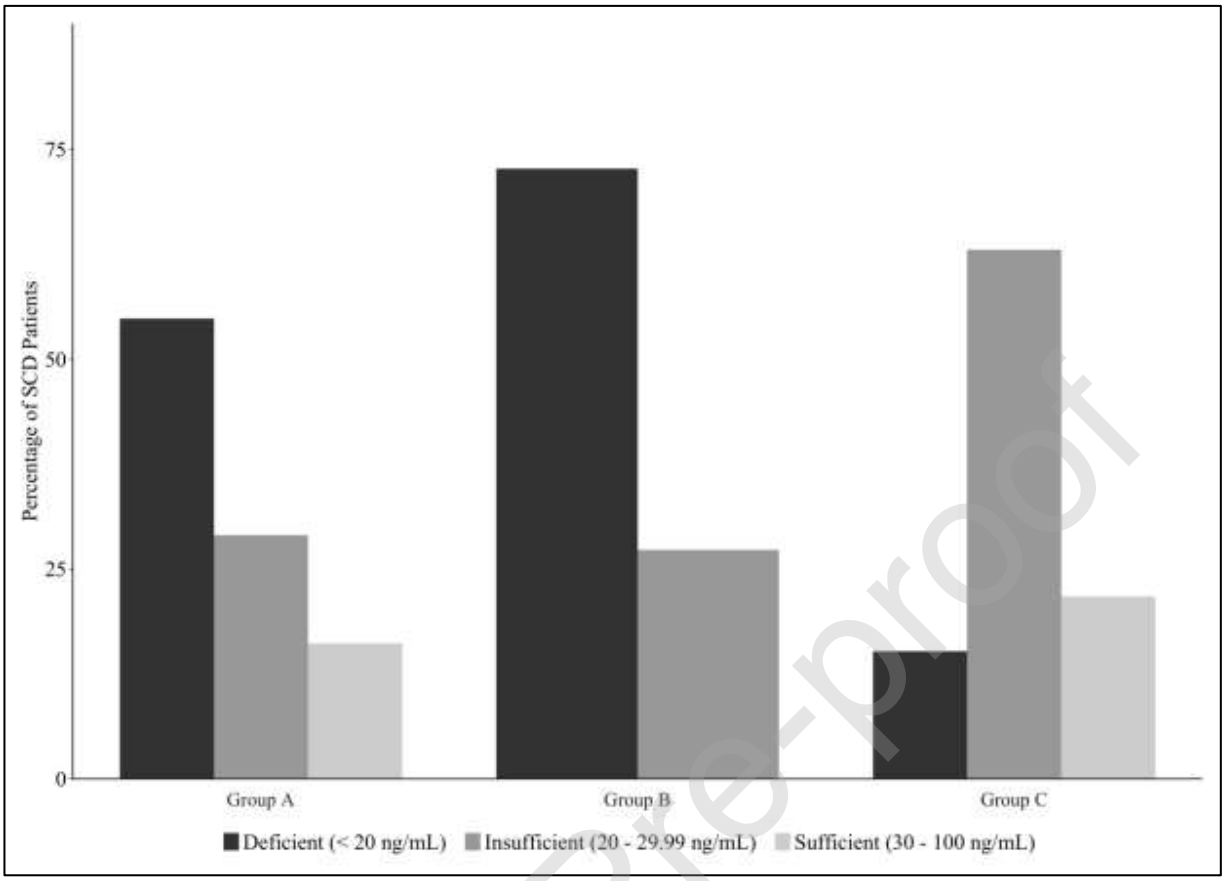

Figure 1. The percentage of SCD patients with deficient, insufficient, and sufficient mean serum 25-OHD levels (ng/mL) separated by vitamin D supplementation status. (a) Group A corresponds to patients who did not receive vitamin D supplementation at any time during the study period. (b) Group B corresponds to patients supplemented with vitamin D, but did not have at least one serum 25-OHD level that was in the sufficient range (≥ 30 ng/mL) during the study period. (c) Group C corresponds to patients supplemented with vitamin D who had at least one serum 25-OHD level that was in the sufficient range (≥ 30 ng/mL) during the study period.

Vitamin D Supplementation and ED Visits

Patients supplemented who reached the sufficient range had on average 10 serum 25-OHD level collected during the study period (range = 1 – 27). Vitamin D supplementation occurred between 2 and 24 months before the sufficient range (≥ 30 ng/mL) was reached.

For Group C (supplemented ≥ 30 ng/mL), the number of ED visits was inversely correlated with mean serum 25-OHD levels (r = -.23, p = .13), although this result did not reach statistical significance. Additionally, we examined whether Group C had more ED visits before they had at

least one serum 25-OHD level in the sufficient range. Analyses demonstrated that Group C had significantly more ED visits before (2.59) compared to after (1.26) reaching sufficiency, $t(45) = 2.29$, $p = .03$, d = .34.

Discussion

Our study evaluated the prevalence of vitamin D deficiency in 110 patients with SCD. The results of our investigation indicated that 45% of patients had vitamin D deficiency. Only 20% of patients had sufficient vitamin D levels. When patients supplemented with vitamin D are excluded, the prevalence of vitamin D deficiency was 55%. In stark contrast, only 15% of patients supplemented who had at least one serum 25-OHD level in the sufficient range had vitamin D deficiency. Thus, our study adds to the growing literature that patients with SCD have significant vitamin D deficiency.[7,32]

Additionally, we explored the relationship between vitamin D supplementation and ED visits after the implementation of a home pain management plan (HPMP) in our sickle cell clinic that successfully reduced uncomplicated pain ED visits.[29] When we compared vitamin D supplemented groups to those patients who did not receive supplementation, no differences between groups were identified. Given that patients in our convenience sample who needed strategies to manage uncomplicated pain had a HPMP, it is possible that we observed a lower number of ED visits for patients who did not receive supplementation because they were better able to manage their pain at home.

However, when patients supplemented with vitamin D in the sufficient range were examined in isolation, we found that fewer ED visits were associated higher mean serum 25-OHD levels. Of particular importance, the number of ED visits was lower after they reached the

sufficient range (≥ 30 ng/mL) than before. This observation highlights the importance of achieving optimal serum 25-OHD levels to reduce the number of pain-related ED visits in the pediatric SCD population.

The precise mechanisms by which vitamin D supplementation lowers the rate of pain-related ED visits remain unclear. Vitamin D deficiency may aggravate the disease process and increase the risk of complications through alteration of neural and immune processes that contribute to the experience of pain.[11] In a rodent model, vitamin D deficiency has been shown to lead to selective alterations in target innervation, resulting in presumptive nociceptor hyperinnervation of skeletal muscle producing mechanical hypersensitivity.[33] In human participants, previous research that has shown that chronic pain is associated with vitamin D deficiency,[23] that 6 months of high dose vitamin D supplementation reduced the number of pain days per week and increased physical activity related quality of life, [16] and that children with deficient serum 25-OHD levels experienced significantly more pain episodes.[20] Additional research is needed, however, to further clarify risk factors and specifically characterize the clinical benefits of vitamin D supplementation.

There are limitations to our study. We included pediatric patients at only one center in the United States and thus, they may not be representative of patients in different states or countries, which reduces the generalizability of the findings. Additionally, we had a smaller sample size, which affected the ability to detect significant effects, if present. The study was also limited by our inability to determine adherence to vitamin D supplementation. Further studies should include monitoring of adherence, as reaching the sufficient vitamin D range was optimal in reducing ED visits. Moreover, because we assessed ED visits over a 6-year period, we were unable to determine whether patients were prescribed HU or were receiving chronic blood transfusion continuously

over the entire study period. This is important, as research has demonstrated that children receiving HU have higher mean serum 25-OHD levels than those not receiving HU.[34]

Conclusion

Vitamin D deficiency is common in the general population particularly in Black/African American populations; however, the consequences of vitamin D deficiency appear to have additional clinical significance in the SCD population. Vitamin D deficiency was observed in 45% of our overall sample and in 55% of the non-supplemented patients. As pain is the leading cause of morbidity and healthcare utilization for patients with SCD[35] our study indicates that vitamin D supplementation to the sufficient range is one complementary treatment to reduce pain-related ED visits. It is therefore recommended that serum 25-OHD screening and supplementation become part of routine care for pediatric patients with SCD.

Funding

Anna Hood was supported in part by a grant from the National Heart, Lung, and Blood Institute, National Institutes of Health (1F32HL143915)

Author Statement

Contribution: A.M.H and L.E.C. designed the experiment, analyzed and interpreted data, and prepared the manuscript. C.T.Q, C.D.K, L.M.S. designed the experiment and prepared the manuscript. J.L.P analyzed and interpreted data. All authors critically reviewed and approved the final version of the manuscript.

Declarations of Interest

None

Acknowledgments

The authors would like to thank the patients and the medical providers at Cincinnati Children's Hospital Medical Center for their cooperation in generating the data needed for this study. The authors would also like to acknowledge Eva Hanson for her assistance with literature review.

References

[1] Hassell KL. Population Estimates of Sickle Cell Disease in the U.S. *Am J Prev Med*. 2010;38(4, Supplement):S512-S521. doi:http://dx.doi.org/10.1016/j.amepre.2009.12.022

[2] Darbari DS, Wang Z, Kwak M, et al. Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study. *PLoS One*. 2013;8(11):e79923.

[3] Wang ZJ, Wilkie DJ, Molokie R. Neurobiological mechanisms of pain in sickle cell disease. *ASH Educ Progr B*. 2010;2010(1):403-408.

[4] Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet*. 2004;364(9442):1343-1360.

[5] Ojelabi A, Graham Y, Ling J. Health-related Quality of Life Predictors in Children and Adolescents with Sickle Cell Disease: A Systematic Review. *Int J Trop Dis Heal*. 2017;22(2):1-14. doi:10.9734/IJTDH/2017/31954

[6] Hildenbrand AK, Nicholls EG, Daly BP, Marsac ML, Tarazi R, Raybagkar D. Psychosocial and pharmacological management of pain in pediatric sickle cell disease. *Postgrad Med*. 2014;126(2):123-133.

[7] Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. *PLoS One*. 2015;10(3):e0119908.

[8] 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(3):797-803.

[9] Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. *Pediatrics*. 2009;124(3):e362.

[10] 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(5):622-627.

[11] Helde-Frankling M, Björkhem-Bergman L. Vitamin D in pain management. *Int J Mol Sci*. 2017;18(10):2170.

[12] Hewison M. Vitamin D and immune function: an overview. *Proc Nutr Soc*. 2012;71(1):50-61.

[13] Straube S, Moore AR, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain*. 2009;141(1):10-13.

[14] Straube S, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev*. 2015;(5).

[15] Shams T, Al Wadani H, El-Masry R, Zakaria O. Effect of prophylactic vitamin D on anesthetic outcome in children with sickle cell disease. *J Anaesthesiol Clin Pharmacol*. 2014;30(1):20.

[16] 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.

[17] Jain D, Jaiswal S, Bakshi N, Krishnamurti L. Frequency of Vasocclusive Crises and the Relationship of Vitamin D Deficiency to the Frequency of Pain Crises in Children with Sickle Cell Disease in an Aboriginal Tribal Region in Gadchiroli, India. 2017.

[18] Hamdy M, Salama N, Maher G, Elrefaee A. Vitamin D and Nonskeletal Complications among Egyptian Sickle Cell Disease Patients. *Adv Hematol*. 2018;2018.

[19] Adegoke SA, Smith OS, Adeniyi AT, Adekile AD. Thrombospondin-1 and Vitamin D in Children With Sickle Cell Anemia. *J Pediatr Hematol Oncol*. 2018.

[20] Adegoke SA, Oyelami OA, Adekile A, Figueiredo MS. Influence of serum 25-

hydroxyvitamin D on the rate of pain episodes in Nigerian children with sickle cell anaemia. *Paediatr Int Child Health*. 2017;37(3):217-221.

[21] AlJama A, AlKhalifah M, Al-Dabbous IA, Alqudaihi G. Vitamin D deficiency in sickle cell disease patients in the Eastern Province of Saudi Arabia. *Ann Saudi Med*. 2018;38(2):130.

[22] 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(4):643-647.

[23] Osunkwo I, Hodgman EI, Cherry K, et al. Vitamin D deficiency and chronic pain in sickle cell disease. *Br J Haematol*. 2011;153(4):538-540.

[24] Mandese V, Bigi E, Bruzzi P, et al. Endocrine and metabolic complications in children and adolescents with Sickle Cell Disease: an Italian cohort study. *BMC Pediatr*. 2019;19(1):56.

[25] Jackson TC, Krauss MJ, DeBaun MR, Strunk RC, Arbeláez AM. Vitamin D deficiency and comorbidities in children with sickle cell anemia. *Pediatr Hematol Oncol*. 2012;29(3):261-266.

[26] Martyres DJ, Vijenthira A, Barrowman N, Harris-Janz S, Chretien C, Klaassen RJ. Nutrient insufficiencies/deficiencies in children with sickle cell disease and its association with increased disease severity. *Pediatr Blood Cancer*. 2016;63(6):1060-1064.

[27] Winters AC, Kethman W, Kruse-Jarres R, Kanter J. Vitamin D insufficiency is a frequent finding in pediatric and adult patients with sickle cell disease and correlates with markers of cell turnover. *J Nutr Disord Ther*. 2014;4(140):2161-05091000140.

[28] McCaskill M, Ogunsakin O, Hottor T, Harville E, Kruse-Jarres R. Serum 25-Hydroxyvitamin D and Diet Mediates Vaso-Occlusive Related Hospitalizations in Sickle-Cell Disease Patients. *Nutrients*. 2018;10(10):1384.

[29] Crosby LE, Simmons K, Kaiser P, et al. Using quality improvement methods to implement an electronic medical record (EMR) supported individualized home pain management plan for children with sickle cell disease. *J Clin outcomes Manag JCOM*. 2014;21(5):210.

[30] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.

[31] R Core Team. R: A language and environment for statistical computing. 2017.

[32] de Oliveira JF, Vicente NG, Santos JPP, Weffort VRS. Vitamin D in children and adolescents with sickle cell disease: an integrative review. *Rev Paul Pediatr (English Ed*. 2015;33(3):349-354.

[33] Tague SE, Clarke GL, Winter MK, McCarson KE, Wright DE, Smith PG. Vitamin D deficiency promotes skeletal muscle hypersensitivity and sensory hyperinnervation. *J Neurosci*. 2011;31(39):13728-13738.

[34] Adegoke SA, Braga JAP, D Adekile A, Figueiredo MS. Impact of Hydroxyurea on Anthropometry and Serum 25-Hydroxyvitamin D Among Children With Sickle Cell Disease. *J Pediatr Hematol Oncol*. 2018;40(4):e243-e247.

[35] Smith WR, Scherer M. Sickle-cell pain: advances in epidemiology and etiology. *ASH Educ Progr B*. 2010;2010(1):409-415.

TABLE 1. Comparison of characteristics of pediatric sickle cell disease patients separated by vitamin D supplementation status

Characteristics	**Group A** No Vitamin D Supplement (n = 31)[1]	**Group B** Vitamin D Supplement < 30 ng/mL (n = 33)	**Group C** Vitamin D Supplement ≥ 30 ng/mL (n = 46)[2]
Mean (SD)			
25-OHD (ng/mL)	20.76 (7.86)	16.46 (5.25)	26.14 (7.31)
Range	5 - 35	8 - 28	13 - 55
Age at first visit (years)	10.39 (2.64)	12.58 (2.80)	11.98 (2.72)
Range	8 - 16	8 - 16	8 - 16
No. of ED visits	2.94 (3.83)	3.82 (4.57)	3.85 (3.13)
Range	1 - 20	1 - 25	1 - 16
Supplementation length (months)	n/a	40.92 (25.87)	39.28 (25.73)
Range	n/a	2 - 83	4 - 87
N (%)			
Gender			
Female	15 (48)	17 (52)	25 (55)
Male	16 (52)	16 (48)	21 (45)
Race/ethnicity			
Black/African-American	26 (100)	37 (100)	47 (100)
SCD genotype			

HbSS	23 (74)	29 (66)	34 (74)
HbSC	8 (26)	8 (24)	10 (22)
HbSβ^+ thalassemia	3 (0)	3 (10)	1 (2)
HbSβ^0 thalassemia	0 (0)	0 (0)	1 (2)

Notes: 25-OHD = serum 25-hydroxyvitamin D levels; ED = emergency department; SCD = sickle cell disease
[1] A majority of SCD patients (> 26) in the non-supplemented group had insufficient or deficient levels of vitamin D.
[2] SCD patients had at least one serum vitamin D level that was sufficient (≥ 30 ng/mL) during the study period.