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Vitamin D Insufficiency, Hemoglobin and Anemia in Children with Chronic Kidney Disease

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Abstract

Background: 25-hydroxyvitamin D (25OHD) deficiency is common in children with chronic kidney disease (CKD). It has been associated with an increased risk for anemia in both healthy US children and in adults with CKD. This association has not been explored in children with CKD.

Study Design: Cross-sectional associations were assessed between 25OHD and hemoglobin and anemia in children with CKD.

Setting & Participants: Children aged 1–16 enrolled in the Chronic Kidney Disease in Children (CKiD) study with mild to moderate kidney dysfunction, with 25OHD measured at baseline (n=580).

Measurements: Hemoglobin (g/dL), or anemia, as (hemoglobin <5% for age and sex).

Results: Of n=580, 334 (57.59%) children were vitamin D insufficient/deficient and 137 (23.62%) were anemic. Of those who were vitamin D insufficient/deficient, 95 (28.44%) were anemic. In the overall cohort, the odds of being anemic was 1.9 times higher (95% CI: 1.22–3.04, p<0.01) in vitamin D insufficient/deficient vs sufficient children, when adjusting for covariates (age, sex, race [black, white or other], BMI, iohexol GFR (iGFR), erythropoietin stimulation agent (ESA) use, iron supplementation use and underlying cause of CKD). Stratified by race, the odds of being anemic was 2.39 times higher (95% CI: 1.41–4.05, p=0.001) in vitamin D insufficient/deficient vs vitamin D sufficient white children. The association between vitamin D status and anemia was not significant in black children.

Conclusions: The data support our hypothesis that vitamin D insufficiency/deficiency increases the odds of anemia in children with CKD. The effect was strong and significant among white, but not black, children.

Keywords

Vitamin D; Hemoglobin; Anemia; Chronic Kidney Disease

Introduction

Deficiency of 25-hydroxyvitamin D (25OHD) is highly prevalent in U.S. children and adolescents, seen in up to 70% of those < 21 years [1,2]. Despite an increased recognition of and treatment of vitamin D deficiency in clinical practice, it continues to be prevalent in children with chronic kidney disease (CKD) as well [1,3,4]. 25OHD plays a crucial role in bone and mineral metabolism, and is increasingly recognized to also have effects on immune function, cell proliferation and differentiation, and cardiovascular function [5,6]. A growing body of evidence suggests that 25OHD deficiency is also associated with an increased risk for anemia [7–20]. In adults with CKD, lower 25OHD levels have been independently associated with lower hemoglobin levels and anemia [11–13]. Vitamin D supplementation has also been associated with decreased erythropoiesis stimulating agent (ESA) dose required to maintain hemoglobin, suggesting that vitamin D plays a role in erythropoiesis [13,14]. A large, population-based cohort study in healthy U.S. children demonstrated that lower 25OHD levels were associated with an increased risk for anemia, independently of other anemia risk factors including obesity, inflammation, socioeconomic status, and nutritional deficiencies including B12, folate, and iron [15]. The 25OHD level at which the risk for anemia increased was noted to be lower in black compared to white children. The association between 25OHD and hemoglobin has not been explored in children with CKD.

The objective for this study was to examine the association between 25OHD status and anemia in children with CKD enrolled in the Chronic Kidney Disease in Children (CKiD) cohort study, and to examine whether the association was modified by race. The public health implications of an association between 25OHD and hemoglobin in children with CKD, if confirmed, are compelling given the prevalence of anemia, its known adverse health consequences, and the fact that 25OHD deficiency can be easily and safely corrected with supplementation in this population.

Methods

Setting & Participants

The CKiD study is a multicenter observational prospective cohort study of children ages 1 to 16 years with mild to moderate CKD recruited from 54 pediatric nephrology centers in North America. Inclusion criteria included an estimated glomerular filtration rate (eGFR) between 30 and 90 ml/min/1.73m² determined by the original Schwartz equation [16]. The CKiD study design and conduct were approved by an external advisory committee appointed by the National Institutes of Health and the Institutional Review Boards at each participating center. Details of the study design and objectives have been previously published [17]. For the current analysis, we included subjects enrolled in Cohort 1 of the CKiD study from April 2005 to October 2007 (n=586). The 580 subjects with 25OHD levels available were included

in the analysis. We evaluated hemoglobin and 25OHD values that were obtained at a study visit that occurred approximately 6 months after enrollment (baseline).

Laboratory Assays

Blood samples were collected using standardized techniques. Hemoglobin was measured locally at clinical sites as part of a complete blood count. Proficiency testing surveys published by the College of American Pathologists demonstrate coefficients of variation of 1–2% for the various instruments performing hemoglobin measurement [18]. The serum concentrations of 25OHD were measured by chemiluminescence immunoassay (DiaSorin LIAISON 25OHD TOTAL Assay); inter-and intra-assay coefficients of variation were 11.2 and 8.1%, respectively [19,20]. GFR at the baseline visit was obtained by direct measurement of plasma iothexol disappearance (GE Healthcare, Amersham Division, Princeton, NJ, USA) [21]. In subjects without iothexol GFR (iGFR) results available, GFR was estimated using the bedside CKiD equation [22]. Intact parathyroid hormone (PTH), serum ferritin, serum iron, and total iron-binding capacity (TIBC) assays were performed in the CKiD central laboratory (University of Rochester, Rochester, NY).

Clinical Variables

Demographic data including age and sex were collected from questionnaires administered during the baseline visit. Race and ethnicity were self-reported. Anemia was defined as hemoglobin less than the 5thile for age and sex based on data from the National Health and Nutrition Examination Survey (NHANES) [23]. Vitamin D status was categorized as either sufficient (25OHD level ≥ 30 ng/mL) or insufficient/deficient (25OHD level < 30 ng/mL). Body mass index (BMI) was calculated from height and weight at the baseline visit. Self-reported medication history was obtained from medication summary data files, using medication lists from the baseline visit. Treatment with ESAs, iron supplements or angiotensin converting enzyme (ACE) inhibitors was categorized as Yes/No. Underlying cause of CKD was classified as glomerular (including focal segmental glomerulosclerosis, hemolytic uremic syndrome and other glomerulonephritides) or non-glomerular (including congenital urologic disease, cystic diseases, and reflux nephropathy and other diagnoses) disease. Iron status markers included serum iron, ferritin, and total iron-binding capacity (TIBC), and all assays were performed at the CKiD central laboratory (University of Rochester, Rochester, NY). Transferrin saturation (TSAT) was calculated as: serum iron/ TIBC x 100.

Statistical Analyses

All statistical analyses were performed with Stata statistical software, version 14.0 (StataCorp, College Station, Texas). The statistical significance level was set at $\alpha=0.05$. Linear regression was used to examine the association between 25OHD concentration (as the independent variable) and hemoglobin (as the dependent variable), and logistic regression was used to examine the association of 25OHD status with anemia (as the dependent variable) adjusting for age, sex, race (black, white or other), BMI, iGFR, ESA use, iron supplementation use and underlying cause of CKD. The analyses were also stratified by race to assess for effect modification of the relationship between vitamin D status and anemia.

Results

Five-hundred eighty children were included in the cross-sectional analysis. The baseline demographic and clinical characteristics of the cohort by 25OHD status is presented in Table 1. Children with 25OHD insufficiency/deficiency were significantly older than those with 25OHD sufficiency [median (IQR) age 13 (9, 15) vs 9 (6, 13)] years, $p<0.001$). There was no difference in sex distribution by 25OHD status. 25OHD insufficient/deficient subjects were also more likely to be black, to have glomerular disease as underlying cause of CKD, to have higher BMI, to have higher PTH, and to be anemic compared to those with sufficient levels. There was no difference in median hemoglobin between 25OHD groups; however, Figure 1 illustrates mean 25OHD level by both anemia status and race, demonstrating that the trend for lower mean 25OHD level in anemic subjects was observed across racial groups, although the difference did not reach statistical significance in black subjects. Figure 2 shows correlations between hemoglobin and 25OHD levels by age. There was a significant correlation between hemoglobin and 25OHD levels for the age groups of 6–8 years ($r=0.25$, $p=0.02$) and 9–11 years ($r=0.31$, $p<0.001$).

Using linear regression adjusted for age, sex, race, BMI, iGFR, ESA use, iron supplementation use, and underlying cause of CKD, we found that each 1ng/mL increase in 25OHD level was associated with a 0.01 g/dL increase in hemoglobin ($p<0.01$). The association between 25OHD status and anemia is presented in Table 2. Using fully adjusted logistic regression, 25OHD insufficient/deficient subjects were 1.9 times as likely to be anemic compared to subjects with sufficient levels in the overall cohort (odds ratio (OR) 1.93, 95%CI 1.22–3.04, $p<0.01$). When stratified by race, white subjects with 25OHD insufficiency/deficiency were more than twice as likely to be anemic (OR 2.39, 95% CI 1.41–4.04, $p=0.001$) compared to those with sufficient levels. Although the magnitude of the observed increase in odds of anemia was similar, the association between 25OHD status and anemia did not reach statistical significance in black subjects (OR 2.2, 95% CI 0.23–21.56, $p=0.49$). Given that the distribution of 25OHD levels was notably lower in black compared to white subjects, we also performed a race-stratified analysis using a lower 25OHD threshold of 20ng/mL to define insufficiency/deficiency, but found no association between levels less than 20ng/mL and risk for anemia in either white or black subjects.

In order to control for a potential contribution of iron deficiency to the observed association between 25OHD deficiency and anemia risk, we conducted a sensitivity analysis in 285 subjects with ferritin and TSAT data available. After additional adjustment for ferritin and TSAT, the odds of anemia remained significantly increased in 25OHD insufficient/deficient vs sufficient children (OR=2.25, 95%CI 1.07–4.76, $p=0.03$.) Additionally, in a subset of 169 subjects in whom data on sunlight exposure (hours of physical activity in the sun per week) were added to the model, the odds of anemia was increased (OR 2.64, 95% CI 0.98–7.14) but not statistically significant ($p>0.05$) among 25OHD insufficient/deficient subjects.

Discussion

The present study demonstrates that children with CKD who were 25OHD insufficient/deficient were twice as likely to be anemic as children with sufficient vitamin D levels. This

association was independent of other anemia risk factors including race, BMI, GFR, and use of medications to treat anemia. Mean hemoglobin was also noted to be higher in 25OHD sufficient compared to insufficient/deficient subjects. Notably, median hemoglobin did not differ significantly by 25OHD group in unadjusted analysis, highlighting the importance of using age- and sex-specific hemoglobin thresholds to define anemia. In addition, in sub-analyses adjusted for markers of iron status and sunlight exposure, the risk of anemia remained significantly increased in 25OHD insufficient/deficient subjects. The magnitude of the greater anemia odds for subjects with 25(OHD) levels < 30 ng/mL is consistent with the results of a previous analysis in more than 10,000 healthy U.S. children using the same threshold for 25OHD insufficiency/deficiency (OR for anemia 1.93 (95% CI 1.21–3.08), despite a significantly smaller sample size in the present analysis [15]. This suggests that the mechanism by which the association between 25OHD and anemia is mediated in healthy children applies in children with CKD, and that the association between 25OHD and anemia may in fact be stronger given our ability to detect a significant association in fewer than 600 children.

In the race-stratified analysis, white subjects with 25OHD insufficiency/deficiency demonstrated a significantly higher odds of anemia compared to those with 25OHD sufficiency. However, among black subjects, although the point estimate for the odds ratio suggested a higher odds of anemia in 25OHD insufficient black subjects, the association did not reach statistical significance. Significance was likely limited by the small number of black subjects in the cohort (15% overall) and the observation that most of the black children (79 of 88) were 25OHD insufficient with 25OHD levels < 30 ng/mL; thus the sample size was too small to detect the association between levels above 30ng/mL and presence of anemia in black children specifically

We selected 30 ng/mL as the threshold for 25OHD sufficiency based on recommendations made by both the Endocrine Society and the 2008 Kidney Disease outcomes Quality Initiative (KDOQI) clinical practice guidelines [24,25]. However, we acknowledge the lack of consensus in the research community regarding the definition of 25OHD insufficiency, due in part to the substantial variability among available vitamin D assays and a lack of standardization of research data [24]. The Institute of Medicine for example defines 25OHD levels of >20 ng/mL as being sufficient [24]. Therefore we performed an additional regression analysis using a threshold of 20 ng/mL to define 25OHD insufficiency, but there was no significant association between odds of anemia and 25OHD levels below vs. above a threshold of 20 ng/mL. We did find a significant linear association between 25OHD and hemoglobin in the cohort overall.

Several possible mechanisms might explain the association of 25OHD deficiency with anemia. Vitamin D and its metabolites are present in many tissues, as are receptors for calcitriol, the active form of vitamin D. Calcitriol production (for regulation of bone-mineral metabolism) takes place via the action of the 1- α -hydroxylase enzyme in renal tissue. However, there are multiple extra-renal sites from which locally-produced calcitriol regulates host-cell DNA and controls the extra-skeletal actions of vitamin D [5,8]. Experimental data suggest that inadequate levels of 25OHD leading to decreased local calcitriol production in the bone marrow may limit erythropoiesis; calcitriol has a direct

proliferative effect on erythroid burst forming units, which is synergistic with endogenously produced erythropoietin, and also upregulates expression of the erythropoietin receptor on erythroid progenitor cells [7–10]. Locally-produced calcitriol also plays a key role in the regulation of immune function by inhibiting the expression of pro-inflammatory cytokines by a variety of immune cells, thus providing negative feedback to prevent excessive inflammation.⁵ The immunomodulatory effects of vitamin D may be central to its role in preventing anemia via modulation of systemic cytokine production, which may in turn suppress specific inflammatory pathways which contribute to the development of anemia, particularly in the context of CKD. Additionally, the iron-regulatory protein hepcidin is upregulated in the setting of inflammation and mediates iron-restricted erythropoiesis; hepcidin may be downregulated by the immunomodulatory effects of vitamin D. A pilot study in 2014 by Bacchetta et al. found that supplementation with a single dose of vitamin D (100,000 IU vitamin D) increased serum 25OHD levels and, within 24 hours, was associated with a 34% decrease in circulating hepcidin levels [26].

In support of the proposed mechanisms above, observational studies in adults with CKD have demonstrated that treating 25OHD deficiency improves anemia management and decreased ESA-resistance. In a cohort of anemic and vitamin D deficient adults with non-dialysis CKD treated with ESAs, correction of vitamin D deficiency with supplementation to raise 25OHD levels to greater than 30 ng/mL was associated with an average 24% decrease in the ESA dose required to maintain hemoglobin levels between 11 and 12 g/dL [27]. In studies of adults on chronic hemodialysis, correction of 25OHD deficiency has also been associated with decreased ESA dose requirements to maintain hemoglobin [28,29]. However to date there have been no large-scale trials of vitamin D supplementation as an adjunctive therapy for anemia in children with CKD.

The public health implications of an association between 25OHD and hemoglobin in children with CKD, if confirmed by future analyses of other CKD cohorts, are compelling. Anemia is highly prevalent in children with CKD and is associated with adverse clinical consequences including increased risk for hospitalization and mortality, increased risk for left ventricular hypertrophy, and decreased quality of life [30–33]. Vitamin D deficiency can be corrected relatively safely, effectively, and inexpensively in children with CKD. It is possible that vitamin D supplementation could be an attractive, adjunctive therapy for anemia beyond the use of ESA and iron supplements.

Our study's strengths include data from a large cohort of children with pre-dialysis CKD from multiple centers across North America with standardized data collection. In addition, GFR was directly measured in the majority of the cohort, and the estimating equation used in the remaining subjects has been shown to be accurate [21]. Our study has several limitations, including a limited sample size of black subjects and the fact that data for iron store markers and sunlight exposure was not available for all subjects.

In conclusion, we find that 25OHD insufficiency/deficiency is associated with a significantly higher odds of anemia in children with CKD. Further studies are needed to clarify the mechanism of this association so that vitamin D supplementation can be potentially utilized as an adjunctive anemia therapy.

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Compliance with ethical standards The CKiD study design and conduct were approved by an external advisory committee appointed by the National Institutes of Health and the Institutional Review Boards at each participating center. Details of the study design and objectives have been previously published

References

1. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML (2009) Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. *Pediatrics* 124:e362–370.
2. Holick MF (2007) Vitamin D deficiency. *N Engl J Med* 357:266–281. [PubMed: 17634462]
3. Atkinson MA, Juraschek SP, Bertenthal MS, Detrick B, Furth SL, Miller ER 3rd (2017) Pilot study of the effect of cholecalciferol supplementation on hepcidin in children with chronic kidney disease: Results of the D-fense Trial. *Pediatr Nephrol* 32:859–868. [PubMed: 28013381]
4. Kumar J, McDermott K, Abraham AB, Friedman LA, Johnson VL, Kaskel FJ, Furth SL, Warady BA, Portale AA, Melamed ML (2016) Prevalence and correlates of 25-hydroxyvitamin D deficiency in the Chronic Kidney Disease in Children (CKiD) cohort. *Pediatr Nephrol* 31:121–129. [PubMed: 26307635]
5. Bikle D (2009) Nonclassic actions of vitamin D. *J Clin Endocrinol Metab* 94:26–34. [PubMed: 18854395]
6. Shroff R, Knott C, Rees L (2010) The virtues of vitamin D—but how much is too much? *Pediatr Nephrol* 25:1607–1620. [PubMed: 20393752]
7. Saab G, Young DO, Gincher Y, Giles K, Norwood K, Coyne DW (2007) Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clin Pract* 105:c132–138. [PubMed: 17228173]
8. Armas LA, Heaney RP (2011) Vitamin D: the iceberg nutrient. *J Ren Nutr* 21:134–139. [PubMed: 21239184]
9. Alon DB, Chaimovitz C, Dvilansky A, Lugassy G, Douvdevani A, Shany S, Nathan I (2002) Novel role of 1,25(OH)(2)D(3) in induction of erythroid progenitor cell proliferation. *Exp Hematol* 30:403–409. [PubMed: 12031646]
10. Aucella F, Scalzulli RP, Gatta G, Vigilante M, Carella AM, Stallone C (2003) Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure. A synergistic effect with r-HuEpo. *Nephron Clin Pract* 95:c121–127. [PubMed: 14694273]
11. Kendrick J, Targher G, Smits G, Chonchol M (2009) 25-hydroxyvitamin D deficiency and inflammation and their association with hemoglobin levels in chronic kidney disease. *Am J Nephrol* 30:64–72. [PubMed: 19218791]
12. Kiss Z, Ambrus C, Almasi C, Berta K, Deak G, Horonyi P, Kiss I, Lakatos P, Marton A, Molnar MZ, Nemeth Z, Szabo A, Mucsi I (2011) Serum 25(OH)-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patients on maintenance hemodialysis. *Nephron Clin Pract* 117:c373–378.
13. Patel NM, Gutierrez OM, Andress DL, Coyne DW, Levin A, Wolf M (2010) Vitamin D deficiency and anemia in early chronic kidney disease. *Kidney Int* 77:715–720. [PubMed: 20130525]
14. Lac PT, Choi K, Liu IA, Meguerditchian S, Rasgon SA, Sim JJ (2010) The effects of changing vitamin D levels on anemia in chronic kidney disease patients: a retrospective cohort review. *Clin Nephrol* 74:25–32. [PubMed: 20557863]
15. Atkinson MA, Melamed ML, Kumar J, Roy CN, Miller ER 3rd, Furth SL, Fadrowski JJ (2014) Vitamin D, race, and risk for anemia in children. *J Pediatr* 164:153–158. [PubMed: 24112861]

16. Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 58:259–263. [PubMed: 951142]
17. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, Wong C, Muñoz A, Warady BA (2006) Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. *Clin J Am Soc Nephrol* 1:1006–1015. [PubMed: 17699320]
18. Fadrowski JJ, Pierce CB, Cole SR, Moxey-Mims M, Warady BA, Furth SL (2008) Hemoglobin decline in children with chronic kidney disease: baseline results from the chronic kidney disease in children prospective cohort study. *Clin J Am Soc Nephrol* 3:457–462. [PubMed: 18235140]
19. Ersfeld DL, Rao DS, Body JJ, Sackrison JL Jr, Miller AB, Parikh N, Eskridge TL, Polinske A, Olson GT, MacFarlane GD (2004) Analytical and clinical validation of the 25 OH vitamin D assay for the LIAISON automated analyzer. *Clin Biochem* 37:867–874. [PubMed: 15369717]
20. Wagner D, Hanwell HE, Vieth R (2009) An evaluation of automated methods for measurement of serum 25-hydroxyvitamin D. *Clin Biochem* 42:1549–1556. [PubMed: 19631201]
21. Schwartz GJ, Furth S, Cole SR, Warady B, Muñoz A (2006) Glomerular filtration rate via plasma iohexol disappearance: pilot study for chronic kidney disease in children. *Kidney Int.* 69:2070–2077. [PubMed: 16612328]
22. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL (2009) New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 20:629–637. [PubMed: 19158356]
23. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C; Centers for Disease Control and Prevention, National Center for Health Statistics (2005) Hematological and iron-related analytes--reference data for persons aged 1 year and over: United States, 1988–94. *Vital Health Stat* 11 247:1–156.
24. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, Thamm M, Tian L, Merkel JM, Jones JC, Carter GD, Sempos CT (2016) Vitamin D measurement standardization: The way out of the chaos. *J Steroid Biochem Mol Biol* 73:117–121.
25. (2009) KDOQI Work Group. KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. executive summary. *Am J Kidney Dis* 53:S11–104.
26. Bacchetta J, Zaritsky JJ, Sea JL, Chun RF, Lisse TS, Zavala K, Nayak A, Wesseling-Perry K, Westerman M, Hollis BW, Salusky IB, Hewison M (2014) Suppression of iron-regulatory hepcidin by vitamin D. *J Am Soc Nephrol* 25:564–572. [PubMed: 24204002]
27. Lac PT, Choi K, Liu IA, Meguerditchian S, Rasgon SA, Sim JJ (2010) The effects of changing vitamin D levels on anemia in chronic kidney disease patients: a retrospective chart review. *Clin Nephrol* 74:25–32. [PubMed: 20557863]
28. Saab G, Young DO, Gincherman Y, Giles K, Norwood K, Coyne DW (2007) Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clin Pract* 105:132–138.
29. Kiss Z, Ambrus C, Almasi C, Berta K, Deak G, Horonyi P, Kiss I, Lakatos P, Marton A, Molnar MZ, Nemeth Z, Szabo A, Mucsi I (2011) Serum 25(OH)D-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patient on maintenance hemodialysis. *Nephron Clin Pract* 117:373–378.
30. Amaral S, Hwang W, Fivush B, Neu A, Frankenfield D, Furth S (2006) Association of mortality and hospitalization with achievement of adult hemoglobin targets in adolescents maintained on hemodialysis. *J Am Soc Nephrol* 17:2878–2885. [PubMed: 16943308]
31. Schaefer F (2008) Cardiac disease in children with mild-to-moderate chronic kidney disease. *Curr Opin Nephrol Hypertens* 17:292–297. [PubMed: 18408481]
32. Mitsnefes MM, Kimball TR, Kartal J, Witt SA, Glascock BJ, Khoury PR, Daniels SR (2006) Progression of left ventricular hypertrophy in children with early chronic kidney disease: 2-year follow-up study. *J Pediatr* 149:671–675. [PubMed: 17095341]
33. Gerson A, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush B, Furth S (2004) Anemia and health-related quality of life in adolescents with chronic kidney disease. *Am J Kidney Dis* 44:1017–1023. [PubMed: 15558522]

Figure 1.
Mean 25OHD by race and anemia status.

Figure 2. Scatterplot of Hemoglobin (g/dL) versus 25OHD (ng/mL) by Age Group at baseline visit, with line of best fit and Pearson's correlation coefficient.

Table 1.

Baseline Characteristics by 25OHD Status^{*}

Median (IQR) or % (n)	25OHD Insufficient/Deficient (n=334)	25OHD Sufficient (n=246)	p-value
Age (yrs)	13(9, 15)	9(6, 13)	<0.001
Male	64.1 (214)	61.8(152)	0.57
Race			<0.001
White	58.4(195)	82.1 (202)	
Black	23.7 (79)	3.7 (9)	
Other	18(60)	14.2(35)	
% Glomerular Disease	31.1 (104)	13.8(34)	<0.001
BMI (kg/m ²)	20.1 (16.7,24.4)	17.2(15.8, 19.3)	<0.001
iGFR(ml/min/1.73m ²)	48.1 (28.9,67.6)	43.1 (28.2,62.9)	0.09
Hemoglobin (g/dL)	12.7(11.6, 13.7)	12.8(11.9, 13.6)	0.37
PTH ^γ (pg/mL)	42.7(17,63.6)	31.8(12.3,55.3)	<0.01
Anemic ^α	28.4 (95)	17.1 (42)	0.001
On ESA ^β	9.9 (33)	10.6(26)	0.79
On iron	23.4 (78)	30.1 (74)	0.07
On ACE ^μ inhibitor	49.1 (164)	47.9(118)	0.79
	n=166	n=109	
Ferritin (ng/mL)	46 (30.5, 79)	34 (23, 63)	0.13
TSAT (%)	22(16,33)	24(16,30)	0.36

^{*} 25OHD status was categorized as either sufficient (25OHD level >30 ng/mL) or insufficient/deficient (25OHD level <30 ng/mL).;

^α Anemia was defined as Hemoglobin less than 5th percentile for age and sex based on data from NHANES;

^β Erythropoiesis stimulating agent;

^γ Parathyroid hormone;

^μ Angiotensin converting enzyme

BMI body mass index, *TSAT* transferrin saturation, *iGFR* iohexol glomerular filtration rate

Table 2.

Logistic regression models demonstrating association between 25OHD status and anemia. 25OHD status was categorized as either sufficient (25OHD level >30 ng/mL) or insufficient/deficient (25OHD level <30 ng/mL).

Risk for Anemia	OR (95% CI)	P-value
Overall, 25OHD sufficient vs insufficient *	1.93(1.22,3.04)	<0.01
By race *		
White	2.39(1.41,4.05)	0.001
Black	22 (0.22, 21.56)	0.49

* Model adjusted for: age, sex, race, BMI, iGFR, ESA supplementation, iron supplementation, underlying cause of CKD.

BMI body mass index, *iGFR* iohexol glomerular filtration rate, *ESA* erythropoiesis stimulating agent, *CKD* chronic kidney disease