Vitamin D Deficiency Is Associated with Pulmonary Exacerbations in Children with Cystic Fibrosis

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Abstract

Rationale: Recent literature suggests vitamin D has an effect on lung function and on the lung's ability to fight infection, both important in the cystic fibrosis (CF) population as predictors of morbidity and mortality.

Objectives: Our study assessed associations between vitamin D and % predicted lung function, pulmonary exacerbations, and first *Pseudomonas aeruginosa* infection in children with CF. We hypothesized that children with CF who have 25-hydroxy vitamin D (25-OHD) levels less than 30 µg/L would have lower % predicted lung function and more pulmonary exacerbations than those with 25-OHD greater than or equal to 30 µg/L.

Methods: This retrospective longitudinal study of 130 children aged 6 to 18 years between 2000 and 2012 examined 25-OHD levels classed in three vitamin D groups: sufficient (≥ 30 µg/L), insufficient (20–29 µg/L), and deficient (< 20 µg/L). Longitudinal models followed individuals' changing vitamin D groups over time to

compare numbers of pulmonary exacerbations (defined by hospitalization), incidence of first *P. aeruginosa* infection, and % predicted lung function. Cross-sectional comparisons between vitamin D groups were performed at ages 8, 12, and 16 years.

Measurements and Main Results: The prevalence of vitamin D deficiency and insufficiency increased slowly through adolescence. The rate of exacerbations for the deficient vitamin D group, aged 15 to 18 years, was 13.1 per 10 patient-years, significantly higher than 4.3 per 10 patient-years for the insufficient and sufficient vitamin D groups ($P < 0.05$), which were not significantly different. There were no differences between vitamin D groups in pulmonary function or incidence of first *P. aeruginosa* infection, which was about 2 per 10 patient-years.

Conclusions: Higher 25-OHD levels in children with CF were associated with lower rates of pulmonary exacerbations and, in adolescents, higher FEV₁.

Keywords: lung diseases; pediatrics; vitamin D

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Recent studies suggest that vitamin D has a role in lung growth, preserving lung function, and preventing pulmonary infection (1–7). The largest study comes from the Third National Health and Nutrition Examination Survey (NHANES III) data, which showed in healthy adults those with the highest 25-hydroxyvitamin

D (25-OHD) levels had significantly higher FVC and FEV₁ than those with the lowest 25-OHD levels (3). In healthy infants and children, vitamin D deficiency has been associated with a higher risk of and more severe respiratory infections (4, 6–8).

Vitamin D deficiency is common in the cystic fibrosis (CF) population and

ranges from 40 to 90%, depending on age and definition of deficiency (9–14). The cause of vitamin D deficiency in CF is multifactorial, including pancreatic insufficiency, reduced sunlight exposure, poor body fat stores, and decreased vitamin D-binding protein (14, 15). Increased risk of vitamin D deficiency

may be intrinsic to the CF transmembrane conductance regulator mutation, as those with CF given high doses of ergocalciferol with pancreatic enzymes have less absorption and impaired conversion to 25-OHD than control subjects (16).

Vitamin D is an important factor to consider in the CF population, where pulmonary function and pulmonary exacerbations are major determinants of morbidity and mortality (17–20). In fact, one study showed that almost 25% of children failed to recover to baseline FEV₁ after hospital admission for a pulmonary exacerbation (21). Studies on vitamin D and lung function in the CF population are lacking. Most studies focus on prevalence of vitamin D deficiency, supplementation, and bone health but comment on lung function as a possible predictor of vitamin D deficiency (22–24). These studies have had conflicting results, with only one study reporting a significant positive relationship between 25-OHD level and pulmonary function (23). Animal studies have suggested that vitamin D deficiency may affect lung function by limiting lung growth (1, 2). *In vitro* studies on CF bronchial epithelial cells have shown that vitamin D up-regulates cathelicidin, an antimicrobial with activity against *Pseudomonas aeruginosa* (25). *P. aeruginosa* infection and colonization are important in CF, as they can significantly decrease lung function and increase morbidity and mortality in this population (18, 26, 27).

The relationship between vitamin D and lung function is still unclear, particularly in the CF population. It is unknown whether vitamin D has a linear dose response or a threshold effect on FVC and FEV₁ as suggested by the NHANES data (3). It is also unknown if vitamin D deficiency is related to other markers of CF lung disease, such as pulmonary exacerbations and age of first detection of *P. aeruginosa* in sputum or oropharyngeal culture. Our study aimed to define the relationship between vitamin D, lung function, and pulmonary exacerbations in children with CF and to determine if there is a threshold level of 25-OHD that optimizes its pulmonary effects. We hypothesized that children with CF and 25-OHD levels less than 20 µg/L and less than 30 µg/L would have lower pulmonary function and more frequent pulmonary exacerbations than those with

25-OHD levels greater than or equal to 30 µg/L.

Methods

Study Subjects

This retrospective longitudinal study analyzed pulmonary function tests (PFT) and 25-OHD in 130 children aged 6 to 18 years between 2000 and 2012, from the University of Minnesota Cystic Fibrosis Center's database. Patients were included if they were (1) diagnosed with CF by positive sweat test, defined as a chloride level greater than 60 mmol/L using pilocarpine iontophoresis, (2) had two known CF gene mutations on different chromosomes, and (3) had at least one 25-OHD measurement and one PFT measurement in the study period. Patients were excluded if they (1) were pancreatic sufficient (17 patients), as they do not have impaired absorption of vitamin D and other fat-soluble vitamins; and (2) had a history of liver transplant (two patients) or lung transplant (eight patients). PFT measurements were excluded from analysis after a patient had evidence of liver dysfunction, because this could affect vitamin D metabolism. Liver dysfunction was defined as an elevated alanine aminotransferase (ALT) or elevated aspartate aminotransferase (AST) three times the upper limit of normal (35 IU/L for girls and 40 IU/L for boys). The study period record for each patient began with their first measurement of 25-OHD between the ages of 6 and 18 years. All subsequent PFTs, measurements of body mass index (BMI) percentile, 25-OHD, and vitamins A and E were included through age 18 years or November 2012, or an elevated ALT or AST. Most patients contributed several years of data to the analysis. The University of Minnesota Institutional Review Board approved the study protocol, and participants had previously given informed consent as part of the database inclusion criteria, permitting their records to be used for research purposes.

Measurements

Pulmonary function testing was performed at outpatient visits using standardized spirometry. Lung function was measured by FEV₁, FVC, and FEV₁/FVC from valid expiratory efforts per American Thoracic

Society Guidelines (28). All FVC and FEV₁ measurements are reported as percent of predicted values, based on NHANES III norms (29). FEV₁/FVC is reported as calculated from the original measurements. Only outpatient PFT results were used as lung function outcomes.

Pulmonary exacerbations were defined as hospitalizations, identified from the longitudinal record by inpatient PFTs. Our database manager verified that PFTs labeled as "inpatient" were consistent with the medical record for hospital admission. Dates for inpatient PFTs were used to define exacerbations as follows: A patient's first inpatient PFT during the study period was considered their first exacerbation, and all subsequent inpatient PFTs within 30 days were assumed to be part of the same hospital-treated exacerbation, because most patients are treated with antibiotics for a 21-day course. The next inpatient PFT more than 30 days later was considered the start of their second exacerbation, and the same 30-day window was applied. This count was performed throughout the patient record during the study period to identify all exacerbations. Inpatient PFTs were used only to identify exacerbations and not included as outcomes in any analysis.

Serum total 25-OHD concentrations were measured as part of CF annual studies, starting at 1 year of age. Measurements of total 25-OHD were performed using liquid chromatography/tandem mass spectrometry. Participants were divided into the following groups based on 25-OHD level: sufficient greater than or equal to 30 µg/L, insufficient 20 to 29 µg/L, and deficient less than 20 µg/L. These definitions were based on published recommendations for defining vitamin D deficiency as 25-OHD less than 20 µg/L and the Cystic Fibrosis Foundation's recommendation for maintaining total 25-OHD levels between 30 µg/L and 60 µg/L (30–32). Vitamin A and vitamin E levels were measured by high-performance liquid chromatography.

Percentile of BMI was calculated using the SAS program from the Centers for Disease Control (<http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm>).

Pseudomonas aeruginosa was detected by routine surveillance sputum and/or oropharyngeal cultures performed quarterly at outpatient clinic visits using standard

clinical microbiological protocols. The date of initial infection was the first detection of *P. aeruginosa* infection on sputum or oropharyngeal culture, recorded in the University of Minnesota Cystic Fibrosis Center's database.

Statistical Methods

In the longitudinal analyses of PFT, exacerbations, and *P. aeruginosa* outcomes, a child's vitamin D group often changed over time. For each child, the longitudinal record was formed by assigning all outcome measurements during each interval between 25-OHD measurements to the vitamin D group of the 25-OHD measurement that started the interval. That is, vitamin D group was carried forward from one 25-OHD measurement to the next 25-OHD measurement. All outcome measurements after an elevated AST-ALT were omitted.

Rates of exacerbation and of first *P. aeruginosa* infection were estimated and compared between groups using Poisson regression for repeated measurements, fit by generalized estimating equations. The model for *P. aeruginosa* infection contained only vitamin D group; the model for exacerbation contained vitamin D group, age group, and their interaction. PFT outcomes were compared using longitudinal regression models, with polynomials in age and a random intercept for each subject to model the mean path for each vitamin D group and a random intercept for each subject to model the correlation between measurements from the same child.

We also report cross-sectional comparisons of vitamin D groups at ages 8, 12, and 16 years, with a single observation from each child. These three ages were chosen to survey the age range and so that each group had at least one child. In the cross-sectional analysis, sex proportions were compared by chi-square, and continuous variables were compared by analysis of variance for categorical vitamin D and linear regression for continuous vitamin D. Finally, simple linear regression was used to model % predicted lung function as response on 25-OHD as a continuous predictor. Analyses were performed in SAS Version 9.3 (SAS Institute 2010, Cary, NC). Figures 1 and 2 were drawn in R (R Foundation for Statistical Computing, 2012, Vienna, Austria. <http://www.R-project.org>).

Figure 1. Percent predicted FVC, FEV₁, and the ratio FEV₁/FVC, age 6 to 18 years. *Light gray line segments* show measurements for each child in the study. *Green curve* (age 6–18 yr) is fitted mean for sufficient vitamin D group; *blue curve* (age 7–18 yr) is fitted mean for insufficient vitamin D group; *red curve* (age 11–18 yr) is fitted mean for deficient vitamin D group. Fitted means are shown only for years in which a group contained at least four children.

Figure 2. Numbers of hospitalizations for exacerbation per 10 patient-years, by vitamin D group and age category. Green line connects rates for sufficient vitamin D group; blue line connects rates for insufficient vitamin D group; red line connects rates for deficient vitamin D group. The rate of exacerbations for the deficient vitamin D group, ages 15 to 18 years (marked *b*), was significantly higher than for the insufficient and sufficient vitamin D groups (marked *a*, $P < 0.05$).

Results

There were 130 children aged 6 to 18 years between 2000 and November 2012 who met inclusion criteria, with a total of 2,247 PFTs and 468 measurements of 25-OHD. Initial 25-OHD levels for the 130 children were distributed roughly equally across ages 6 to 18 years, with median longitudinal record of 4 years. The proportions of children with insufficient or deficient 25-OHD increased slowly through adolescence: among children age 6 to 10 years, less than 5% were deficient and 10 to 20% were insufficient; among children 15 to 18 years, about 10% were deficient and 30% were insufficient (Table 1).

Cross-sectional Comparison of Vitamin D Groups at Ages 8, 12, and 16 Years

There were 28, 47, and 51 children with PFT measurements during their 8th, 12th, and 16th year, respectively. Comparison of the vitamin D groups at each age for PFT and nutritional outcomes are shown in Table 1. There were no differences at any of the ages in sex proportion, PFT outcomes, or BMI percentile. Vitamins A and E were significantly lower in the deficient vitamin D group than in the

sufficient vitamin D for 16-year-olds, and this also held for vitamin E in 12-year-olds.

As part of the cross-sectional comparison, linear regression of % predicted FEV₁ on 25-OHD, without adjustment, found that in 16-year-olds, a 10-μg/L increase in 25-OHD was associated with an increase in predicted FEV₁ of 5.5% (95% confidence interval [CI], 0.5–10.5%; $P = 0.036$), but the association was not statistically significant in the 8- and 12-year-olds.

Longitudinal Comparison of Lung Function among Vitamin D Groups

Longitudinal comparison of vitamin D groups is shown in Figure 1, which illustrates the highly variable PFT responses of individuals over even short periods of time. There were no significant differences in mean FEV₁, FVC, or FEV₁/FVC ratio between vitamin D groups, and the differences between estimated mean curves were much smaller than the decline in PFT with age.

Pulmonary Exacerbations and First Detection of *P. aeruginosa* Infection Rates

Numbers of patients hospitalized with pulmonary exacerbations per 10

patient-years, by vitamin D group and age category, are shown in Figure 2. The rate of exacerbations for the deficient vitamin D group, aged 15 to 18 years, was 13 per 10 patient-years (95% CI, 6–31), significantly higher than 4.3 per 10 patient-years (95% CI, 2–8) for the insufficient and sufficient vitamin D groups ($P = 0.041$ and $P = 0.035$, respectively).

Most of the children had their first *P. aeruginosa* infection before the beginning of their record during the study period, leaving only 48 (37%) who were at risk during the study period. For these 48, the incidence of *P. aeruginosa* infection was about 2 per 10 patient-years, with no difference between vitamin D groups.

Discussion

We expected a relationship between vitamin D deficiency and lung function but were surprised to find a stronger association between vitamin D deficiency and number of pulmonary exacerbations. We found that in children aged 15 to 18 years with CF, those with total 25-OHD levels greater than or equal to 20 μg/L have significantly fewer pulmonary exacerbations than those with total 25-OHD levels less than 20 μg/L. This is important in the management of CF, wherein pulmonary exacerbations have been shown at various ages to negatively impact lung function, increase mortality, and decrease quality of life (18, 20, 21). We did not see a significant difference in pulmonary exacerbations between those with vitamin D levels greater than or equal to 30 μg/L and those with vitamin D levels 20 to 29 μg/L, as originally hypothesized. We also noted only a significant linear relationship between vitamin D and FEV₁ over time in adolescents as well. This suggests that vitamin D deficiency may have a cumulative effect over time.

The mechanism by which vitamin D may prevent pulmonary exacerbations could be related to protection from viral infection. Viral infections, including respiratory syncytial virus, influenza A, influenza B, and rhinovirus, are a significant cause of pulmonary exacerbations in children with CF, accounting for up to 60% of exacerbations (33–35). Multiple

Table 1. Cross-sectional comparison of vitamin D categories in children aged 8, 12, and 16 years

	Age (yr)	Deficient (≤ 20 $\mu\text{g/L}$)	Insufficient (20–29 $\mu\text{g/L}$)	Sufficient (≥ 30 $\mu\text{g/L}$)	P Value
No. (% age total)	8	1 (4)	3 (11)	24 (86)	
	12	5 (11)	15 (32)	27 (57)	
	16	7 (14)	14 (27)	30 (59)	
25-OHD, $\mu\text{g/L}$	8	17	21 $\pm$ 1	39 $\pm$ 6	
	12	16 $\pm$ 3	26 $\pm$ 3	36 $\pm$ 7	
	16	15 $\pm$ 4	25 $\pm$ 3	38 $\pm$ 6	
% Male	8	100	33	54	0.505
	12	60	40	60	0.463
	16	71	50	53	0.626
FEV ₁ % predicted	8	104	91 $\pm$ 27	107 $\pm$ 18	0.410
	12	88 $\pm$ 17	89 $\pm$ 19	95 $\pm$ 15	0.418
	16	87 $\pm$ 15	88 $\pm$ 18	100 $\pm$ 18	0.072
FVC% predicted	8	96	110 $\pm$ 6	109 $\pm$ 14	0.647
	12	94 $\pm$ 13	95 $\pm$ 17	98 $\pm$ 14	0.750
	16	98 $\pm$ 13	96 $\pm$ 20	106 $\pm$ 15	0.145
FEV ₁ /FVC	8	0.90	0.74 $\pm$ 0.26	0.85 $\pm$ 0.10	0.300
	12	0.82 $\pm$ 0.13	0.83 $\pm$ 0.07	0.86 $\pm$ 0.07	0.397
	16	0.77 $\pm$ 0.09	0.80 $\pm$ 0.07	0.82 $\pm$ 0.08	0.442
BMI percentile	8	22.9	66 $\pm$ 11	61 $\pm$ 28	0.366
	12	45 $\pm$ 28	41 $\pm$ 25	51 $\pm$ 21	0.395
	16	47 $\pm$ 34	49 $\pm$ 30	51 $\pm$ 21	0.910
Vitamin A, mg/L	8	0.48	0.36 $\pm$ 0.05	0.46 $\pm$ 0.11	0.407
	12	0.43 $\pm$ 0.10	0.43 $\pm$ 0.05	0.48 $\pm$ 0.15	0.480
	16	0.44 $\pm$ 0.09 <i>a</i>	0.54 $\pm$ 0.17 <i>a</i>	0.62 $\pm$ 0.18 <i>b</i>	0.092
Vitamin E, mg/L	8	8.1	8.9 $\pm$ 2	12.1 $\pm$ 4	0.290
	12	6.6 $\pm$ 1 <i>a</i>	9.0 $\pm$ 4 <i>b</i>	11.4 $\pm$ 4 <i>b</i>	0.016
	16	6.3 $\pm$ 2 <i>a</i>	9.5 $\pm$ 3 <i>a</i>	10.7 $\pm$ 3 <i>b</i>	0.030

Definition of abbreviation: 25-OHD = 25-hydroxy vitamin D; BMI = body mass index.

Values are mean $\pm$ SD or n (%). P values are from overall comparison. For each outcome within each age, Vitamin D groups were compared by pairwise linear contrasts. Means or percents with no letters in common (*a* or *b*) were significantly different ($P < 0.05$).

studies have demonstrated a link between vitamin D deficiency and an increased risk of viral illness (4–7). Data from NHANES III showed that in those aged 12 years and older, 25-OHD levels were inversely related to the risk of recent upper respiratory tract infection (4). In addition, those with 25-OHD levels less than 10 $\mu\text{g/L}$ had a 55% higher likelihood of developing an upper respiratory tract infection than those with serum levels greater than or equal to 30 $\mu\text{g/L}$ (4). A randomized, placebo-controlled trial in school children found a lower incidence of influenza A in children treated with vitamin D compared with those treated with placebo during the influenza season (5). In infants, it has been shown that low vitamin D in cord blood samples at birth is associated with higher incidence of respiratory syncytial virus (6), and infants readmitted to the neonatal intensive care unit with acute lower respiratory tract infection had lower vitamin D levels than age-matched control subjects (7). In adults with CF, those who received a high dose of cholecalciferol (250,000 IU)

once at the time of admission for a pulmonary exacerbation had significantly fewer hospitalizations for pulmonary exacerbations over the next 6 months compared with those receiving placebo (36). Combined, these studies suggest that vitamin D may prevent viral infection and possibly work as an adjunct treatment to antibiotics to decrease the severity of an exacerbation.

To our knowledge, this is the first retrospective study describing the longitudinal relationship between vitamin D and lung function as well as other markers of pulmonary disease such as pulmonary exacerbations and pseudomonas acquisition in children with CF. Other studies have examined the prevalence of vitamin D deficiency in CF and examined its association with FEV₁ cross-sectionally. Similar to our results, most of these studies have found no association between vitamin D deficiency and FEV₁ (10, 12, 23, 37). We did, however, see a linear relationship between vitamin D level and FEV₁ in the adolescent age group. The former studies

may not have seen a linear relationship, as they did not adjust for age, and two had a mean age of 9 and 11 years, younger than the adolescent population with significant findings in our study (12, 37). In the third study, 81% of patients were vitamin D deficient or insufficient and may not have had enough patients with 25-OHD levels greater than 30 $\mu\text{g/L}$ to see a significant trend. Similar to our findings in adolescents, one study reported a significant positive linear relationship between vitamin D and FEV₁ (23). Although we did not find a statistically significant difference in lung function using defined thresholds in the younger age groups, FEV₁ ranged from 3 to 13% higher in the sufficient group compared with the deficient group. Although this is not statistically significant, its potential clinical relevance should not be overlooked, particularly in a population whose FEV₁ declines, on average, by 1 to 3% per year (38).

It is unclear why the prevalence of vitamin D deficiency increases with age. This has been found in both

healthy adolescent-aged children and adolescents with CF (10, 12, 39). One would speculate change in dietary habits, such as decreased milk and increased soda consumption. Poor compliance with medications is seen in adolescents, although in our patients vitamin A and E were within normal limits, suggesting compliance with vitamin supplementation. BMI was also normal, suggesting proper nutrition and less severe disease (40).

Study Limitations

This was a retrospective study of patients from a single clinical center. One of our primary outcomes, exacerbation, has no consensus definition. We were limited to counting exacerbations requiring hospitalization, not exacerbations treated at home, and thus underestimated actual rates of exacerbation. Our small sample size prevented adjustment for BMI percentile, 25-OHD supplementation, seasonal differences in 25-OHD, sex, microbiology, other therapies, or other confounders, although BMI, the most

important confounder, was similar in all three vitamin D groups. The sample size for first *P. aeruginosa* infection was less than one-half our study sample, because most children in the study had experienced their first *P. aeruginosa* infection before the beginning of the study period at age 6. Our results are not generalizable to patients with CF with sufficient pancreatic function, because we excluded these patients from our analyses. Last, we did not have information on the treatment of vitamin D deficiency, which may be viewed as a confounder in that those receiving treatment may be followed more closely in clinic. In our clinic, though, those on treatment usually are reevaluated during their routine quarterly visits to determine changes in vitamin D supplementation. However, the strengths of this study are the longitudinal assessment and that it is the first study we know of designed specifically to describe the relationship between vitamin D deficiency and other markers of CF-related pulmonary disease, such as pulmonary exacerbations and

P. aeruginosa infection in children with CF.

In conclusion, our study showed that 25-OHD level less than or equal to 20 µg/L in children with CF is associated with a three times higher rate of pulmonary exacerbations than those sufficient in vitamin D. In addition, in adolescents with CF, a higher vitamin D level was associated with higher FEV₁. Therefore, it is possible that treatment with vitamin D may preserve lung function and improve quality of life in children with CF. Controlled clinical trials are needed to determine the impact of vitamin D on lung function and its role in preventing pulmonary exacerbations in individuals with CF. Multicenter studies with a larger sample size are needed to confirm these findings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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