Effect of Vitamin D and Inhaled Corticosteroid Treatment on Lung Function in Children

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Rationale: Low vitamin D levels are associated with asthma and decreased airway responsiveness. Treatment with inhaled corticosteroids improves airway responsiveness and asthma control.

Objectives: To assess the effect of vitamin D levels on prebronchodilator FEV₁, bronchodilator response, and responsiveness to methacholine (PC₂₀, provocative concentration of methacholine producing a 20% decline in FEV₁) in patients with asthma treated with inhaled corticosteroids.

Methods: We measured 25-hydroxyvitamin D levels in the serum of children with persistent asthma at the time of enrollment in the Childhood Asthma Management Program. We divided subjects into the vitamin D sufficiency (>30 ng/ml), insufficiency (20–30 ng/ml), and deficiency (<20 ng/ml) groups. Covariates included age, treatment, sex, body mass index, race, history of emergency department visits, hospitalizations, and season that vitamin D specimen was drawn. Our main outcome measures were change in prebronchodilator FEV₁, bronchodilator response, and PC₂₀ from enrollment to 8–12 months.

Measurements and Main Results: Of the 1,024 subjects, 663 (65%) were vitamin D sufficient, 260 (25%) were insufficient, and 101 (10%) were deficient. Vitamin D-deficient subjects were more likely to be older, African American, and have a higher body mass index compared with the vitamin D-sufficient and insufficient subjects. In the inhaled corticosteroid treatment group, prebronchodilator FEV₁ increased from randomization to 12 months by 140 ml in the vitamin D-deficient group and prebronchodilator FEV₁ increased by 330 ml in the vitamin D insufficiency group and by 290 ml in the vitamin D sufficiency group ($P = 0.0072$), in adjusted models.

Conclusions: In children with asthma treated with inhaled corticosteroids, vitamin D deficiency is associated with poorer lung function than in children with vitamin D insufficiency or sufficiency.

Keywords: asthma; vitamin D; lung function; forced expiratory volume; children

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Low vitamin D levels are associated with asthma and decreased airway responsiveness.

What This Study Adds to the Field

This study suggests that vitamin D sufficiency in patients treated with inhaled corticosteroids is associated with improved lung function in patients with mild to moderate persistent asthma. When treating patients with persistent asthma with inhaled corticosteroids, vitamin D levels should be monitored.

Levels of prevalence of both asthma, the most common chronic illness in children (1), and vitamin D deficiency have dramatically increased, suggesting they may be linked (2, 3). Multiple studies have supported the hypothesis that asthma and vitamin D deficiency are related (2, 3), but few studies have examined the direct effects of vitamin D levels and corticosteroid treatment on lung function in children with asthma.

Low levels of vitamin D are associated with reduced lung function in adults. An analysis of cross-sectional data from the Third National Health and Nutrition Examination Survey found that serum vitamin D was associated with FEV₁ in a general population (4). Li and colleagues found that in adults with asthma, serum vitamin D levels were positively correlated with FEV₁, FEV₁ percent predicted, and the ratio of FEV₁ to FVC (5). In children, low vitamin D levels have been found to be associated with increased frequency of asthma exacerbations (6) and increased markers of allergy and asthma severity (7, 8).

Treatment with inhaled corticosteroids improves airway responsiveness and asthma control (9). Furthermore, use of inhaled corticosteroids is inversely correlated with vitamin D levels (10). An experimental model of corticosteroid resistance suggested that vitamin D may restore the immunosuppressive function of dexamethasone (10). Thus, vitamin D supplementation may further accentuate the antiinflammatory function of corticosteroids in patients with asthma (10). If vitamin D levels improve lung function in children, then treatment with inhaled corticosteroids may potentiate this effect, but this has not been demonstrated clinically.

We hypothesize that vitamin D levels may modulate the effect of inhaled corticosteroids on lung function and airway responsiveness. The objectives of this study were to assess whether vitamin D levels modulate the effect of inhaled corticosteroids on prebronchodilator FEV₁, bronchodilator response to inhaled β -agonists (BDR), and methacholine challenge test results (PC₂₀; provocative

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*A complete list of members may be found before the beginning of the REFERENCES.

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concentration of methacholine producing a 20% decline in FEV₁).

METHODS

Design

We conducted an analysis using data from the Childhood Asthma Management Program (CAMP), a multicenter trial of 1,041 children with mild to moderate persistent asthma between the ages of 5 and 12 years who were randomly assigned to receive budesonide (inhaled corticosteroid), nedocromil, or placebo. Details of the CAMP clinical trial have been published (9). The institutional review board at the eight participating institutions approved the study (9).

Data Collection

Nurse coordinators obtained spirometric measurements on the subjects before and after bronchodilator administration at randomization and at 12 months. BDR was calculated at each visit as FEV₁ [(postbronchodilator FEV₁ – prebronchodilator FEV₁)/prebronchodilator FEV₁]. Subject airway responsiveness to methacholine was measured by calculating the concentration of methacholine that caused a 20% decrease in the FEV₁ at randomization and 8 months after randomization (PC₂₀ was not measured at the 12-mo postrandomization visit). The concentration that provoked a 20% decrease from postdiluent FEV₁ was obtained by linear interpolation of logarithmic dose–response curve expressed as PC₂₀. Race/ethnicity, family income, and parental education

were determined by parental self-report. Body mass index (BMI) was calculated on the basis of height and weight measurements at randomization.

Serum levels of 25-hydroxyvitamin D (referred to as vitamin D) are thought to be the best circulating biomarker of vitamin D metabolic status and reflect contributions from all sources of vitamin D, including diet and sun exposure (11). A single measurement of vitamin D was obtained on 1,024 subjects (98% of enrolled subjects) by a radioimmunoassay method using stored serum samples that had been frozen since randomization (12, 13), as previously reported (6). We categorized vitamin D levels as deficient (≤ 20 ng/ml), insufficient (20–30 ng/ml), and sufficient (> 30 ng/ml), based on previous studies (14).

Our main outcome measures were the change in BDR and prebronchodilator FEV₁ from randomization to 12 months and log PC₂₀ between randomization and 8 months. We chose to study the change in our outcome measurements over 8–12 months to capture the effects of both treatment and vitamin D level on lung function. We chose to study the first 8–12 months of the CAMP clinical trial because the maximal effect of inhaled corticosteroids on BDR was seen at 12 months and vitamin D levels were available at randomization (9).

Statistical Analyses

Analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC; 2007). In bivariate analyses, we evaluated the association of vitamin D sufficiency, insufficiency, or deficiency and independent variables. We studied the association of vitamin D sufficiency, insufficiency, or deficiency with our main outcome measures prebronchodilator FEV₁,

TABLE 1. BASELINE DEMOGRAPHIC VARIABLES STRATIFIED BY VITAMIN D DEFICIENCY, INSUFFICIENCY, AND SUFFICIENCY

	Vitamin D Sufficiency (n = 663)	Vitamin D Insufficiency (n = 260)	Vitamin D Deficiency (n = 101)	P Value
Age, yr [SD]*	8.76 [2.10]	9.10 [2.17]	9.71 [1.98]	<0.0001
Treatment group†				0.03
Inhaled corticosteroid	71% (216)	23% (69)	7% (20)	
Nedocromil	59% (182)	29% (89)	12% (36)	
Placebo	64% (265)	25% (182)	11% (45)	
Sex†				0.39
Male	66% (405)	24% (146)	10% (60)	
Female	62% (258)	28% (114)	10% (41)	
Weight, kg [SD]*	32.1 [11.2]	34.5 [12.5]	39.0 [14.3]	<0.0001
Height, cm [SD]*	132.4 [13.7]	134.8 [14.1]	138.0 [13.3]	0.0003
Body mass index, kg/m ² [SD]*	17.8 [3.2]	18.5 [3.7]	19.8 [4.3]	<0.0001
Race†				<0.0001
White	72% (507)	23% (159)	5% (34)	
African American	34% (46)	31% (41)	35% (47)	
Hispanic	63% (62)	27% (26)	10% (10)	
Other	52% (48)	37% (34)	11% (10)	
Education†				0.81
High school or less	66% (121)	24% (43)	10% (19)	
Some college	65% (542)	26% (216)	10% (82)	
Income†‡				0.42
<\$30,000/yr	64% (152)	25% (59)	12% (28)	
≥\$30,000/yr	65% (488)	26% (192)	9% (66)	
History of ED visits†				0.026
Absent	67% (457)	23% (155)	10% (66)	
Present	59% (206)	30% (105)	10% (35)	
Hospitalization history†				0.88
Absent	65% (598)	25% (232)	10% (90)	
Present	63% (65)	27% (28)	11% (11)	
Season that vitamin D level was drawn†				<0.0001
Winter	59% (126)	24% (52)	17% (36)	
Spring	54% (181)	33% (112)	13% (43)	
Summer	77% (222)	18% (51)	6% (16)	
Fall	67% (124)	25% (47)	8% (14)	

Definition of abbreviation: ED = emergency department.

Total number of subjects: 1,024.

Vitamin D deficiency, ≤ 20 ng/ml; vitamin D insufficiency, 20–30 ng/ml; and vitamin D sufficiency, > 30 ng/ml.

* For continuous measures, means and standard deviations in square brackets are provided.

† Percentages given are relative to categories in the left column.

‡ Data were not available for all subjects.

TABLE 2. LUNG FUNCTION BY VITAMIN D DEFICIENCY FROM 8 TO 12 MONTHS

Vitamin D Status		12 Months				8 Months	
		Prebronchodilator FEV ₁ (L/s)	P Value	BDR	P Value	Log PC ₂₀	P Value
Inhaled corticosteroid	Vitamin D sufficient, n = 210	1.93 [0.73]	0.88	0.073 [0.06]	0.45	4.91 [8.40]	0.55
	Vitamin D insufficient, n = 66	2.01 [0.65]		0.072 [0.071]		4.22 [7.95]	
	Vitamin D deficient, n = 20	1.97 [0.43]		0.085 [0.083]		6.35 [11.45]	
Nedocromil	Vitamin D sufficient, n = 180	1.84 [0.55]	0.95	0.10 [0.087]	0.83	5.42 [9.81]	0.58
	Vitamin D insufficient, n = 85	1.90 [0.57]		0.11 [0.11]		3.47 [6.54]	
	Vitamin D deficient, n = 36	1.85 [0.54]		0.11 [0.13]		5.85 [9.57]	
Placebo	Vitamin D sufficient, n = 255	1.85 [0.53]	0.33	0.10 [0.094]	0.52	3.23 [5.83]	0.30
	Vitamin D insufficient, n = 99	1.88 [0.58]		0.12 [0.13]		3.03 [5.10]	
	Vitamin D deficient, n = 43	1.94 [0.67]		0.12 [0.096]		4.56 [8.35]	

Definition of abbreviation: BDR = bronchodilator response to inhaled β -agonists; PC₂₀ = provocative concentration of methacholine producing a 20% decline in FEV₁.

Total number of subjects: 1,024.

Means and standard deviations in square brackets are provided.

BDR, and log PC₂₀. We studied the association of the change in each of our outcome measures from randomization to 8 months (PC₂₀) or 1 year (prebronchodilator FEV₁, BDR) in all of the treatment groups. In multivariate analyses using least-squares means regression, we built forced-entry models with the variables significant at $P \leq 0.20$, which included age, race, BMI, history of emergency department (ED) visit, sex, and season that vitamin D specimen was drawn. Variables significant at $P \leq 0.10$ were retained in the final multivariable models.

RESULTS

Baseline

Of the 1,041 subjects in the trial, 1,024 (98%) subjects had serum vitamin D measurements at randomization, and 663 (65%) of these subjects were vitamin D sufficient, 260 (25%) were vitamin D insufficient, and 101 (10%) were vitamin D deficient. As shown in Table 1, the subjects in the vitamin D–deficient group were older than the subjects in vitamin D–sufficient and insufficient groups (mean age, 9.71 yr vs. 8.76 and 9.10 yr; $P < 0.0001$). The mean weight of subjects with vitamin D deficiency was 39.0 kg, which was significantly more than vitamin D–sufficient and insufficient subjects who weighed 32.1 and 34.5 kg, respectively ($P < 0.0001$). The mean height of vitamin D–deficient subjects was 138 cm, which was significantly taller than vitamin D–sufficient and insufficient subjects, who had a mean height of 132 and 135 cm, respectively ($P = 0.0003$). Vitamin D–deficient subjects had higher BMI at 19.8 kg/m² compared with 17.8 kg/m² in vitamin D–sufficient subjects and 18.5 kg/m² in vitamin D–insufficient subjects ($P < 0.0001$). African American subjects (35%) were more likely to be vitamin D deficient than white (5%), Hispanic (10%), and other (11%) subjects ($P < 0.0001$). Fewer subjects in the inhaled corticosteroid treatment group were vitamin D deficient (7%) compared with the nedocromil (12%) and placebo

(11%) groups ($P = 0.03$). Subjects who had their blood drawn for vitamin D levels in the summer or fall were more likely to be in the vitamin D–sufficient group, with 77% of subjects who had vitamin D levels drawn in the summer being in the vitamin D–sufficient group and 67% for subjects who had levels drawn in the fall. In comparison, 59% of subjects who had vitamin D levels drawn in the winter and 54% of subjects with levels drawn in the spring were in the vitamin D–sufficient group ($P < 0.0001$). There were no differences in vitamin D sufficiency, insufficiency, or deficiency by sex, parental education, household income, or history of hospitalizations. Subjects who had a history of experiencing ED visits were more likely to be vitamin D sufficient (59% were vitamin D sufficient whereas 30% were vitamin D insufficient); however, of subjects who did not have a history of ED visits, 67% were vitamin D sufficient and 23% were vitamin D insufficient ($P = 0.026$).

Follow-up

As shown in Table 2, there were no differences in prebronchodilator FEV₁, BDR, and log PC₂₀ at 8 to 12 months by vitamin D sufficiency, insufficiency, or deficiency group. Even after stratifying by treatment group, there were no differences in these parameters.

No differences were seen in the change in prebronchodilator FEV₁, BDR, and log PC₂₀ at 8 to 12 months when comparing the vitamin D groups when all treatment groups were combined. Furthermore, the changes in BDR and PC₂₀ were similar for the budesonide, nedocromil, and placebo groups.

Table 3 shows the change in prebronchodilator FEV₁ by vitamin D categories in the entire CAMP population over the first year of the trial. In subjects treated with inhaled corticosteroids, adjusted (age, sex, race, BMI, history of ED visit, season

TABLE 3. CHANGE IN PREBRONCHODILATOR FEV₁ BETWEEN RANDOMIZATION AND 12 MONTHS BY VITAMIN D DEFICIENCY

Treatment Group	Vitamin D Sufficient: Mean Change in Prebronchodilator FEV ₁ (L/s) (n = 663)	Vitamin D Insufficient		Vitamin D Deficient	
		Mean Change in Prebronchodilator FEV ₁ (L/s) (n = 260)	P Value*	Mean Change in Prebronchodilator FEV ₁ (L/s) (n = 101)	P Value*
Inhaled corticosteroid, n = 305	0.30 [0.023]	0.33 [0.031]	0.45	0.14 [0.057]	0.0072
Nedocromil, n = 307	0.19 [0.039]	0.17 [0.028]	0.18	0.25 [0.023]	0.83
Placebo, n = 412	0.23 [0.020]	0.24 [0.025]	0.54	0.16 [0.033]	0.06

Definition of abbreviation: BDR = bronchodilator response to inhaled β -agonists; PC₂₀ = provocative concentration of methacholine producing a 20% decline in FEV₁.

Total number of subjects: 1,024.

Means and standard deviations in square brackets are provided.

*Adjusted for age, sex, body mass index, history of emergency department visit, race, and season that vitamin D specimen was drawn. Reference group is vitamin D–sufficient group. Entries in boldface indicate statistical significance.

that vitamin D specimen was drawn) least-squares regression demonstrated that being vitamin D sufficient or insufficient was associated with greater prebronchodilator FEV₁ change over 12 months compared with the vitamin D-deficient group. When treated with inhaled corticosteroids while being vitamin D sufficient, subjects experienced an increase of 0.30 L in prebronchodilator FEV₁, whereas when treated with inhaled corticosteroids, vitamin D-insufficient subjects experienced an increase of 0.31 L, and subjects who were vitamin D deficient experienced an increase of 0.14 L in prebronchodilator FEV₁ ($P = 0.0072$). We conducted a similar analysis with FEV₁ percent predicted as the main outcome and we found similar results. When treated with inhaled corticosteroids while being vitamin D sufficient, subjects experienced an increase of 5.2% in prebronchodilator FEV₁ percent predicted whereas when treated with inhaled corticosteroids, vitamin D-insufficient subjects experienced an increase of 6.1%, and subjects who were vitamin D deficient experienced a decrease of 1.5% in prebronchodilator FEV₁ percent predicted ($P = 0.036$). Figure 1 depicts the change in prebronchodilator FEV₁ and prebronchodilator FEV₁ percent predicted from randomization to 12 months in the subjects treated with inhaled corticosteroids for the vitamin D deficiency, insufficiency, and sufficiency groups, while adjusting for age, sex, race, BMI, and history of ED visit. Adjusted (age, sex, race, BMI, history of ED visit, season that vitamin D level was drawn) least-squares regression demonstrated that in the inhaled corticosteroid group, the change in BDR decreased by 0.035 over 12 months for subjects who were vitamin D sufficient whereas the change in BDR decreased by 0.057 in subjects who were vitamin D insufficient, and increased by 0.0053 for subjects who were vitamin D deficient; however, this finding did not reach statistical significance ($P = 0.10$). We explored whether there was a linear relationship between vitamin D level and change in prebronchodilator FEV₁, BDR, and PC₂₀, and did not find a relationship after adjusting for age, sex, race, BMI, history of ED visit, and season that vitamin D level was drawn.

DISCUSSION

Prior work in children has supported a role for vitamin D in preventing asthma exacerbations in children in the CAMP trial, especially those children treated with inhaled corticosteroids (6). Our current study found that children with asthma who are deficient in vitamin D levels have less improvement in prebronchodilator FEV₁ over the course of 1 year when treated with inhaled corticosteroids as compared with children who are sufficient in vitamin D. These findings support the hypothesis that vitamin D supplementation may enhance the antiinflammatory function of corticosteroids in patients with asthma.

Strengths of our study include a well-characterized cohort of children with asthma, ascertainment of vitamin D levels at randomization, and carefully measured lung function measures. Our bivariate results that found older age, African American race, and higher BMI are associated with lower vitamin D levels have been seen in previous studies (14, 15). Multiple previous studies have found that inhaled corticosteroids improve lung function (16). Our finding that children who are vitamin D deficient are more likely to have lower lung function is consistent with a previous study that demonstrated that in children with exercise-induced bronchoconstriction, lower vitamin D levels were associated with reduced lung function (17). Our study's result that children with asthma who are vitamin D sufficient have improved lung function is also supported by other studies. Searing and colleagues found that vitamin D levels were associated with FEV₁ percent predicted and FEV₁/FVC ratio; however, they had a small sample size of 59 subjects with spirometric

Figure 1. Change in (A) prebronchodilator FEV₁ and (B) prebronchodilator FEV₁ percent predicted from randomization to 12 months for vitamin D deficiency (solid line, $n = 20$), insufficiency (dotted line, $n = 69$), and sufficiency (dashed line, $n = 216$) groups, while adjusting for age, sex, race, body mass index, history of emergency department visit, and season that vitamin D level was drawn in patients treated with inhaled corticosteroids. The differences in prebronchodilator FEV₁ and prebronchodilator FEV₁ percent predicted for the vitamin D groups were obtained by multivariate analyses using least-squares means regression. As demonstrated in (A), the change in prebronchodilator FEV₁ for the vitamin D deficiency group ($P = 0.0072$) is significantly less than for the vitamin D-sufficient group (reference group). The change in prebronchodilator FEV₁ for the vitamin D insufficiency group is not significantly different from that for the vitamin D-sufficient group ($P = 0.45$). There were no significant differences in baseline prebronchodilator FEV₁ values between the groups at randomization. (B) Similar results are shown for prebronchodilator FEV₁ percent predicted in subjects treated with inhaled corticosteroids. Vitamin D-sufficient subjects experienced an increase of 5.2% in prebronchodilator FEV₁ percent predicted, vitamin D-insufficient subjects experienced an increase of 6.1%, and subjects who were vitamin D deficient experienced a decrease of 1.5% in prebronchodilator FEV₁ percent predicted ($P = 0.036$ compared with vitamin D-sufficient group).

results and they did not have longitudinal measures (10). The apparent paradox of the decrease in BDR over time in vitamin D-sufficient versus vitamin D-deficient subjects is appropriate because as prebronchodilator FEV₁ increases, BDR decreases (i.e., subjects are maximally dilated at baseline) (18).

Our findings are supported by Sutherland and colleagues, who found that reduced vitamin D levels are associated with impaired lung function, especially in adults who are not being treated with inhaled corticosteroids (19). The authors suggested that vitamin D supplementation could be especially beneficial in patients who are not treated with inhaled corticosteroids (19). *In vitro* studies also support the findings of our study. Searing

and colleagues found that vitamin D potentiates glucocorticoid action in peripheral blood mononuclear cells *in vitro* (10).

Despite the strengths of our study, some caveats deserve mention. We chose to study children who are vitamin D deficient compared with children who are vitamin D insufficient and sufficient; however, the sample size of children who were vitamin D deficient was relatively small, with 101 subjects. The number of subjects who were vitamin D deficient and in the inhaled corticosteroid arm was even smaller. Nevertheless, this sample size is larger than in previous studies (10). Furthermore, a high proportion of the vitamin D-deficient group was African American, and in addition, a high proportion of inhaled corticosteroid-resistant patients with asthma was African American. This finding is consistent with vitamin D biology, in which high melanin content in the skin limits ultraviolet B light absorption, which is the major biological source of vitamin D. Race and skin color are not confounders in our analysis because they are in the causal pathway defining low vitamin D (20).

In addition, our sample size was not large enough to conduct our analyses stratified by race, although we did adjust for race in our analyses. On the basis of the biology described previously, this is probably an overadjustment and hence conservative. Future prospective studies will help address these questions. Other limitations include that we studied vitamin D levels at only one time point; given the low reproducibility of vitamin D levels this would likely be a null bias and would have biased our results in a direction of not finding a significant effect of vitamin D on lung function. A prospective study to validate findings is needed. Furthermore, we did not find a dose-response relationship between vitamin D levels and change in FEV₁, BDR, or PC₂₀; however, we did not expect to be able to assess a dose-response relationship because the CAMP population does not have a full range of vitamin D levels in the vitamin D sufficiency category with a mean level of 37.8 ng/ml (SD 15.7).

In conclusion, vitamin D sufficiency in patients treated with inhaled corticosteroids is associated with improved lung function in patients with mild to moderate persistent asthma. Monitoring vitamin D levels and/or supplementing with vitamin D could be considered during inhaled corticosteroid treatment for patients with asthma.

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CAMP Credit Roster

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