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The Association between Vitamin D Status and the Rate of Exacerbations Requiring Oral Corticosteroids in Preschool Children with Recurrent Wheezing

Avraham Beigelman, MD, MSCI^a, Robert S. Zeiger, MD, PhD^{b,c}, David Mauger, PhD^d, Robert C. Strunk, MD^a, Daniel J. Jackson, MD^e, Fernando D. Martinez, MD^f, Wayne J. Morgan, MD, CM^f, Ronina Covar, MD^g, Stanley J Szeffler, MD^g, Lynn M. Taussig, MD^h, Leonard B. Bacharier, MD^a, and for the Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute

^aDepartment of Pediatrics, Washington University and St. Louis Children's Hospital, St. Louis, MO

^bDepartment of Allergy, Kaiser Permanente Southern California, San Diego, CA

^cDepartment of Pediatrics, University of California – La Jolla, CA

^dDepartment of Public Health Sciences, Pennsylvania State University, Hershey, PA

^eDepartments of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI

^fArizona Respiratory Center, University of Arizona, Tucson, AZ

^gDepartment of Pediatrics, Divisions of Pediatric Clinical Pharmacology and Allergy and Immunology, National Jewish Health and University of Colorado School of Medicine, Denver, CO

^hDepartment of Pediatrics, National Jewish Health and University of Denver, Denver, CO

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To the Editor:

Preschool children with recurrent yet intermittent wheezing experience substantial disease morbidity that is primarily related to acute and often severe exacerbations^{E1}. Recent epidemiological data suggest that vitamin D status may modulate the risk of these wheezing exacerbations, as vitamin D levels are inversely associated with adverse asthma-related

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Corresponding Author: Avraham Beigelman, M.D. Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine. 660 S. Euclid Ave. Campus Box 8116 St. Louis, MO 63110 Phone (314) 454-2694 Fax (314) 454-2515 beigelman_a@kids.wustl.edu.

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outcomes among older children and adolescents^{1, 2}. To the best of our knowledge, no study has evaluated whether vitamin D deficiency during early life is a risk factor for exacerbation of wheezing episode among preschool children who already developed the recurrent wheezing phenotype. We conducted this *post-hoc* analysis to investigate whether deficient serum vitamin D levels were associated with an increase in the rate of wheezing exacerbations requiring oral corticosteroid (OCS) among a well-defined cohort of preschool children with severe intermittent wheezing participating in the Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddler (MIST) clinical trial of the Childhood Asthma Research and Education (CARE) Network³.

A detailed description of the MIST trial³, study population, clinical outcome measurements, vitamin D measurements, analysis plan, sample size and power calculations could be found in the Methods section in this article's Online Repository at www.jacionline.org.

Briefly, MIST³ was a one year multicenter, double-blind, randomized trial comparing daily low dose budesonide inhalation suspension to intermittent high-dose budesonide starting at the early signs of Respiratory Tract Illness (RTI), for the prevention of severe respiratory exacerbations requiring OCS. Participants were children 12-53 months of age with history of recurrent severe wheezing. All participants had risk factors for future asthma, as evidenced by a positive modified Asthma Predictive Index (mAPI^{E2}). Institutional review boards at all participating centers approved the MIST protocol, and parents provided written informed consent. The primary outcome measure of MIST, as well as this *post hoc* analysis, was the rate of severe respiratory exacerbations, requiring OCS (prednisolone), over the one-year study period³, which did not differ between the daily low-dose and intermittent high dose regimens of inhaled budesonide³.

There is a lack of consensus as to the optimal levels of 25-OH-VitD to define vitamin D status for conditions other than for the maintenance of bone health, for which The Institute of Medicine recommends a serum 25-OH-VitD levels of at least 20 ng/mL⁴. Moreover, there is a lack of consensus concerning the normal or optimal vitamin D serum levels in various ethnic groups as it was recently reported that compared to Caucasians, African American adults had lower total serum vitamin D levels, but these African Americans had similar estimated concentrations of bioavailable vitamin D resulting from lower levels of Vitamin D binding protein⁵. Previous asthma studies have detected associations between vitamin D levels and asthma outcomes using different serum vitamin D cutoff levels among older children^{1, 2}. Due to these uncertainties in defining the appropriate vitamin D cutoffs for respiratory health, the lack of consensus concerning the normal vitamin D serum levels in various ethnic groups, and the absence of previous studies that investigated the relationships between serum vitamin D levels and asthma-related outcomes in preschool children, our primary analysis considered 25-OHVitD level as a continuous variable, whereas secondary analyses were performed using 25-OHVitD as a dichotomous variable, with a 25-OH-VitD cutoff of 20 ng/ml.

Baseline serum vitamin D levels were measured in 264 (95%) of the 278 children enrolled in the MIST trial. The mean (SD) age of the patients was 35 ($\pm$ 11) months, 69% of the participants were males, and 62% were Caucasian (Table 1). The median (Q1, Q3) 25-OH-

VitD level was 33.5ng/ml (26.4, 43.7).. Eighteen participants (7%) had 25-OH-VitD levels below 20 ng/ml (i.e., vitamin D deficiency). Vitamin D deficient participants were more often non-Caucasian (72% vs 36%, $p=0.002$) and reported tobacco smoke exposure (72% vs 41%, $p=0.010$), compared to the non-deficient participants (Table 1). Vitamin D deficiency was more common in samples obtained in winter and fall seasons, although these differences were only marginally significant (Table 1).

25-OH-VitD level (as a continuous variable) at the time of study randomization was not associated with the rate of exacerbations requiring OCS therapy over the one-year trial (pseudo r -square = 0.006, $p=0.65$).

Vitamin D deficient participants had a significantly higher mean rate of exacerbations requiring OCS than non-deficient participants (1.46 vs. 0.93 exacerbations/child-year, $p=0.035$; rate ratio 1.56, 95% CI 1.03-2.37). Due to the relatively small number of participants with vitamin D deficiency, adjustment for covariates that significantly differed between the vitamin D deficient and non-deficient groups was performed for each covariate one at a time (one model included adjustment for race and additional model included adjustment for tobacco smoke exposure), rather than simultaneously. The rate ratio for OCS treatment remained significant after adjustment for race and smoke exposure (Table 2). Multiple secondary outcomes did not differ between participants with vitamin D levels < 20 ng/ml and participants with vitamin D levels $\geq$ 20 ng/ml (Table E1): the rate of RTIs, the rate of RTIs in which a viral etiology was detected by multiplex PCR in the nasal samples obtained during the acute episode (viral RTIs), the rates of ED or urgent care visits, and the proportion of episodes free-days (EFDs) over the 12 month trial, defined as days without any respiratory symptoms and without use of albuterol. We did not detect interactions between MIST study treatment assignment or race and vitamin D deficiency status on the rate of exacerbations ($p=0.3$ and $p=0.6$, respectively). Stratification by race showed that both Caucasian and non-Caucasian participants that were vitamin D deficient had numerically higher mean rates of exacerbations requiring OCS compared to non-deficient children; however, this difference was statistically significant only among non-Caucasians (Table E2). The lack of statistical significance in the rate of exacerbations among Caucasians is most likely a reflection of reduced statistical power to detect such a difference among Caucasians, only 5 of whom were vitamin D deficient. However, we cannot definitively exclude a differential effect of vitamin D deficiency based on race, as low serum vitamin D levels among African Americans and Caucasians might have different clinical significance resulting from different levels of vitamin D binding proteins among these 2 ethnic groups⁵.

To the best of our knowledge, this is the first study to demonstrate an association between vitamin D deficiency and significant exacerbations among preschool children with severe but intermittent wheezing, corroborating the findings of increased asthma morbidity among vitamin D deficient school age children and adolescents with persistent asthma^{1, 2}. Our findings demonstrate that the relationship between significant exacerbations and vitamin D status was evident when a level of 25-OH-vitamin D was used as the cutoff of 20 ng/ml, whereas no association was demonstrated using 25-OH-VitD as a continuous measure, suggesting a threshold effect of vitamin D level on the outcome of exacerbations in this age

group where serum vitamin D levels of at least 20 ng/ml may be adequate to attenuate the risk of exacerbations, while higher levels may not provide any additional benefits.

Vitamin D deficiency in the US was reported to be less common among young children compared to older children and adolescent⁶. Accordingly, the prevalence of vitamin D deficiency in our study was only slightly lower than the 12% prevalence reported among 2 independent cohorts of preschool children in North America: 380 children in the US⁷ and 508 children in Canada⁸. Lower prevalence of vitamin D deficiency among toddlers in North America might be related to routine vitamin D supplementation among this age group and/or to the presence of vitamin D supplements in dairy products. Our study also revealed a substantially higher prevalence of vitamin D deficiency among non-Caucasians, which is in agreement with the epidemiology of vitamin D deficiency². However, a recent report has questioned the clinical significance of low total serum vitamin D levels among African American adults⁵.

Our study has the advantages of utilizing a well characterized cohort of preschool children with severe intermittent wheezing and positive mAPI, and of a direct measurement of vitamin D status in participants at study inception as opposed to previous studies which have estimated early life vitamin D status indirectly by measuring maternal serum or cord blood vitamin D levels^{E3-E5}. These previous studies yielded conflicting results regarding the association between maternal vitamin D status and the development of the wheezing phenotype during early life^{E3-E5}. Some study limitations exist. Since vitamin D deficiency was relatively infrequent in MIST, we adjusted for the most relevant potential confounders (race and tobacco smoke exposure) one at a time using separate models rather than analyzing both confounders simultaneously in a single, unstable model. The low number of vitamin D deficient participants at each CARE center precluded adjustment for study center due to multivariate model instability. Therefore, although unlikely, we cannot definitively exclude residual bias that contributes to detection of a higher rate of exacerbations among the vitamin D deficient children. Since our primary outcome was the rate of exacerbations assessed over the year of the study, which exposed all participants to seasonal variations in vitamin D levels, we did not adjust the rate of severe exacerbation by season at enrollment despite marginally significant variability in the prevalence of vitamin D deficiency by season of enrolment. Finally, based on the cross-sectional nature of this analysis, we cannot determine if the relationship between vitamin D deficiency and exacerbations noted in this study is causal, nor can we exclude the possible contributions of other factors, such as diet, activity, or other environmental exposures.

In summary, vitamin D deficiency in preschool children with severe intermittent wheezing treated with ICS therapy was associated with a higher rate of exacerbations requiring OCS. While the association between vitamin D deficiency and exacerbations was statistically significant only among African American children, the relevance of these ethnic differences remains uncertain since the use of single reference value to discriminate vitamin D deficiency in Caucasians and African Americans may be inappropriate⁵. The association between vitamin D levels and the risk of exacerbations was significant only among children with serum 25-OH-VitD levels <20 ng/ml, suggesting that future studies of vitamin D

supplementation as an intervention for the prevention of wheezing episodes might need to focus on this subgroup of children.

Methods

Study participants

The Childhood Asthma Research and Education (CARE) Network performed a post-hoc retrospective analysis of data from the Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddler (MIST) clinical trial¹. Detailed descriptions of the screening, recruitment, design, outcomes, and statistical analysis for the MIST trial have been reported in detail elsewhere¹. Briefly, MIST¹ was a one year multicenter, double-blind, randomized trial comparing daily low dose budesonide inhalation suspension (0.5 mg nightly) to intermittent high-dose budesonide inhalation suspension (1 mg twice daily for seven days) starting at the early signs of Respiratory Tract Illness (RTI), for the prevention of severe respiratory exacerbations requiring oral corticosteroids (OCS).

Participants were children 12-53 months of age with recurrent wheezing who experienced at least four episodes of wheezing in the year prior to randomization (or at least 3 episodes if treated with an asthma controller medication for at least 3 months) with at least one exacerbation requiring the use of systemic corticosteroids, urgent care visit, or hospitalization in the prior year. All participants had risk factors for future asthma, as evidenced by a positive modified Asthma Predictive Index (mAPI²). Children with persistent asthma symptoms were ineligible to participate. The MIST study results showed that a daily low-dose regimen of inhaled budesonide was not superior to an intermittent high dose regimen of inhaled budesonide in reducing exacerbations¹.

Institutional review boards at all participating centers approved the MIST protocol, and parents provided written informed consent.

Outcome measures

The primary outcome measure of MIST and the outcome of this post-hoc analysis was the rate of severe respiratory exacerbations over the one-year study period. A severe exacerbation was defined as an episode of lower respiratory tract symptoms for which an oral glucocorticoid (prednisolone) was started following consultation with a study physician (by telephone or in person) according to a specific protocol^{1, 3, 4}.

The Institute of Medicine concluded that serum 25-OH-VitD levels of at least 20 ng/mL are sufficient to maintain appropriate bone health⁵. However, there is a lack of consensus as to the optimal levels of 25-OH-VitD to define vitamin D status for conditions other than bone health. Previous asthma studies among older children have detected associations with asthma outcomes using serum vitamin D cutoff levels of 20 ng/mL (vitamin D deficiency)⁶, 30 ng/mL⁷⁻⁹, or while considering vitamin D as a continuous variable¹⁰. Due to these uncertainties in determining the appropriate vitamin D cutoffs, along with the absence of previous studies that investigated serum vitamin D levels on asthma-related outcomes in preschool children, our primary analysis investigated the association between 25-OH-VitD level as a continuous variable and the study outcomes. In addition, given the possibility of a

threshold effect of 25-OH-VitD levels on respiratory outcomes, we then performed analyses using 25-OH-VitD as a dichotomous variable, with a 25-OH-VitD cutoff of 20 ng/ml.

Vitamin D level measurements

Vitamin D levels were measured in serum samples obtained on enrollment using a direct competitive chemiluminescence immunoassay using the DiaSorin LIAISON 25OHD Total assay^{11, 12}

Analysis plan, sample size and power calculations

Regression models were used to examine potential relationships between baseline Vitamin D levels and the study outcomes. Log-linear regression models based on the Poisson distribution were utilized for the frequency of exacerbations. The length of follow-up time from randomization to study termination was used as an offset so that model results could be interpreted as rates per child year. Strength of association was quantified by the R-squared statistics for the ordinary linear regression models and by the pseudo R-squared statistics for the Poisson regression models¹³. Secondary analyses examining vitamin D as a dichotomous variable utilized Poisson regression models for frequency outcome and analysis of variance for continuous outcomes. The total sample size was fixed by availability of serum samples. Power calculations based on the observed rate of exacerbations in MIST indicated that a sample size of 264 would provide 90% power to detect a relative rate less than 0.83 or greater than 1.2 per 20ng/ml change in Vitamin D. All analyses were carried out using the SAS statistical software system version 9.2 (SAS Inc., Cary NC).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of study population

	All participants (n=264)	Participants with baseline serum 25-OH-vitamin D < 20 ng/ml (n=18)	Participants with baseline serum 25-OH-vitamin D ≥ 20 ng/ml (n=246)	p-value
Younger children (12-32 months)*	120 (45.5%)	7 (38.9%)	113 (45.9%)	0.56
Gender (male)*	184 (69.7%)	13 (72.2%)	171 (69.5%)	0.81
Race (Caucasian)*	163 (61.7%)	5 (27.8%)	158 (64.2%)	<0.01
Height (cm)	94.2 ± 8.9	93.4 ± 8.9	94.3 ± 9	0.75
Weight (kg)	15.3 ± 3.1	15.1 ± 3.3	15.3 ± 3.1	0.60
Physician diagnosis of asthma*	188 (71.2%)	15 (83.3%)	173 (70.3%)	0.24
Rate of wheezing episodes per child in the past yr	6.6 ± 5.4	6.1 ± 2.6	6.7 ± 5.6	0.95
Rate of urgent/ED visits per child in the past yr	4.9 ± 4.2	6.3 ± 4.5	4.8 ± 4.2	0.08
Hospitalization in the past year*	50 (18.9%)	5 (27.8%)	45 (18.3%)	0.32
Tobacco smoke exposure*	113 (43.3%)	13 (72.2%)	100 (41.2%)	0.01
Any asthma controller use in the past year*	184 (69.7%)	13 (72.2%)	171 (69.5%)	0.81
Received oral corticosteroid in the past year*	199 (75.4%)	12 (66.7%)	187 (76%)	0.37
1 positive Food Skin Test*	95 (36.5%)	9 (52.9%)	86 (35.4%)	0.15
1 positive Aeroallergen Skin Test*	153 (58.4%)	13 (72.2%)	140 (57.4%)	0.22
1 positive Aeroallergen Skin Test to outdoor allergen*	120 (45.5%)	10 (55.6%)	110 (44.7%)	0.38
1 positive Aeroallergen Skin Test to indoor allergen*	98 (37.1%)	6 (33.3%)	92 (37.4%)	0.73
Serum IgE (median; Q1, Q3 (kU/L))	58.8 (21.5, 183.7)	82.5 (39.1, 343.2)	55.3 (20.2, 166.8)	0.06
Percent Eosinophil in CBC (median; Q1, Q3)	3.1 (2, 6)	3 (2, 8)	3.1 (2, 6)	0.61
Child ever had eczema*	141 (53.4%)	12 (66.7%)	129 (52.4%)	0.24
Presence of Allergic rhinitis*	101 (38.3%)	9 (50%)	92 (37.4%)	0.29
Parental history of asthma*	160 (63.5%)	15 (83.3%)	145 (62%)	0.07
FeNO (ppb) (median; Q1, Q3)	8.6 (5.7, 14)	6.3 (3.9, 19.5)	8.6 (5.7, 14)	0.54
Percent Episode Free Days	66.9 ± 29.6	77.3 ± 22.5	66.2 ± 29.9	0.16
Randomized to intermittent	132 (50%)	12 (66.7%)	120 (48.8%)	0.14

	All participants (n=264)	Participants with baseline serum 25-OH-vitamin D < 20 ng/ml (n=18)	Participants with baseline serum 25-OH-vitamin D 20 ng/ml (n=246)	p-value
treatment arm [*]				
Family keep a cat or a dog [*]	121 (45.8%)	5 (27.8%)	116 (47.2%)	0.11
Season during which serum was obtained (season at enrollment) [*] :				
Winter (December-February):	57 (22%)	6 (33%)	51 (21%)	0.05
Spring (March- May)	76 (29%)	2 (11%)	74 (30%)	
Summer (June-August)	66 (25%)	2 (11%)	64 (26%)	
Fall (September-November)	65 (25%)	8 (44%)	57 (23%)	
Sites [*]				
Albuquerque, NM	10 (4%)	2 (11%)	8 (3%)	0.02
Denver, CO	43 (16%)	1 (6%)	42 (17%)	
Madison, WI	35 (13%)	0 (0%)	35 (13%)	
San Diego, CA	40 (15%)	1 (6%)	39 (16%)	
St. Louis, MO	74 (28%)	10 (56%)	64 (26%)	
Tucson, AZ	62 (23%)	4 (22%)	58 (24%)	

Data are expressed as means (SE), except as noted.

^{*} Data are expressed as number (%)

Table 2

Rate ratios (95% CIs) of exacerbations requiring OCS among the children with 25-OH-VitD levels <20 ng/ml relative to children with 25-OH-VitD levels ≥ 20 ng/ml

Rate ratio	Rate ratio* of exacerbations requiring OCS	95% CI	P-value
Unadjusted	1.56	1.03-2.37	0.035
Adjusted for:			
Race	1.68	1.09-2.58	0.019
Tobacco smoke exposure	1.57	1.02-2.40	0.038

* The rate ratio represents the ratio between the rate of exacerbations requiring OCS among the vitamin D deficient group and the rate of exacerbations requiring OCS among the non- deficient group.