Vitamin D and Asthma: Association, Causality, or Intervention?

Hengameh Raissy, PharmD,¹ and Kathryn Blake, PharmD²

Many observational studies have investigated the potential association between vitamin D and asthma. However, it is difficult to find a temporal causal relationship in cross-sectional or observational studies. This review presents recent clinical trials and the evidence of association between vitamin D and asthma in different patient populations and asthma status. Well-designed clinical trials are warranted in order to define the optimal level of vitamin D, as well as dosing and duration of vitamin D supplementation, in pediatric patients.

THERE HAS BEEN an increase in the number of publications investigating the association between vitamin D and many diseases, including asthma. The relationship between vitamin D and asthma can be explored in several ways: potential role in primary prevention, improvement of lung function, protection against or reduction of asthma morbidity, and enhancement of clinical response to corticosteroids. Upon review of the recent data, it is important to note that vitamin D deficiency or insufficiency, as measured by 25-hydroxyvitamin D (25-OH-VitD) in the serum, has been defined differently across the various trials. The optimal level of 25-OH-VitD for nonmusculoskeletal conditions and for different ethnicities remains controversial and unclear.¹ The Institute of Medicine recommends at least 20 ng/mL of 25-OH-VitD for the maintenance of bone health.²

Vitamin D concentration during pregnancy and risk of developing pulmonary diseases has been a topic of discussion. The results of studies measuring maternal vitamin D or cord blood at the time of delivery have provided conflicting results, from inverse to positive associations with risk of childhood wheezing or developing childhood asthma.³

In a large longitudinal study of children in Australia,⁴ the association between vitamin D status at 6 years of age and development of asthma at 14 years of age was investigated in 693 children in a subgroup analysis. The authors reported a predictive association between vitamin D at age 6 and asthma at age 14 years; the association was essentially confined to males when the data were stratified for sex. A birth cohort study in the Netherlands⁵ reported the cross-sectional and prospective associations between vitamin D status and prevalence of asthma in childhood. Data were

available for a subgroup of 4 year olds ($n=72$) and a subgroup of 8 year olds ($n=328$). Interestingly, vitamin D concentration at 4 years of age was inversely associated with asthma at 4–8 years of age. However, vitamin D at 8 years of age was positively associated with asthma at the same age. The association between vitamin D status early on and the risk for developing asthma in school age children remains unclear.

Several similar epidemiologic studies suggest an inverse association between vitamin D concentration and asthma-related outcomes.^{6,7} In a cross-sectional study of 100 patients aged between 0 and 18 years of age with asthma, 47% had insufficient vitamin D concentrations defined as <30 ng/mL.⁸ Use of oral and inhaled corticosteroids taken over 30 days before the vitamin D measurement showed a significant inverse relationship with vitamin D. A significant positive correlation was reported between forced expiratory volume in first second (FEV1) percent predicted and FEV1/forced vital capacity (FVC) with vitamin D level. These results suggest that vitamin D insufficiency may be a cause of greater need for therapy in patients with asthma.

The association between vitamin D status and severe asthma exacerbations was evaluated in the Childhood Asthma Management Program (CAMP) study where 25-OH-Vit D concentrations were collected from 1,024 in children 5–12 years of age with mild to moderate persistent asthma at the time of the enrollment.^{9,10} Patients were randomly assigned to budesonide, nedocromil, or placebo, and were followed for a mean of 4.3 years. For the purpose of this analysis, severe asthma exacerbation was defined as any emergency department (ED) visit or hospitalization for

¹Department of Pediatrics, School of Medicine, University of New Mexico, Albuquerque, New Mexico.

²Biomedical Research Department, Nemours Children's Clinic, Jacksonville, Florida.

asthma during the study. Vitamin D insufficiency was defined as 25-OH-VitD <30 ng/mL. Thirty-five percent of children were vitamin D insufficient. Adjusted for age, sex, body mass index, income, and treatment group, the odds of any ED visits or hospitalizations due to asthma was significantly higher in the vitamin D insufficient children over the 4 years of the CAMP trial (odds ratio 1.5 [95% confidence interval 1.1–1.9], $p=0.01$). The association between vitamin D insufficiency and severe asthma exacerbation was also evaluated in a year before the study enrollment, and the odds ratio remained significantly higher in the vitamin D insufficient children. There were no significant differences in skin test reactivity, eosinophils count, or total serum IgE levels between the vitamin D sufficient and insufficient children. There was also no difference in the odds of having prednisone bursts during the 4 years of the CAMP trial. These results suggest that sufficient vitamin D may not prevent exacerbations but it may decrease the severity of exacerbations, hence reducing ED visits or hospitalization due to asthma.

In a recent publication, vitamin D deficiency was investigated as a risk factor for exacerbations of wheezing episodes in preschool children. A *post hoc* analysis was done in a well-defined cohort of preschool children with severe intermittent asthma.^{11,12} The details of the original study and primary outcomes have been discussed previously.¹³ Briefly, in this multicenter, double-blind, randomized clinical trial, 264 children 12–53 months old were randomly assigned to daily low-dose budesonide inhalation suspension or intermittent use of high-dose budesonide inhalation suspension at the early signs of a respiratory tract illness.¹¹ Patients were followed for 1 year, and the primary outcome was asthma exacerbation requiring use of oral corticosteroids. Vitamin D status was assessed in 95% of the patients at baseline, and vitamin D deficiency was defined as 25-OH-VitD <20 ng/mL.¹² There was a significantly higher rate of exacerbation in patients with vitamin D deficiency compared to those with sufficient vitamin D (1.46 vs. 0.93 exacerbation/child-year, $p=0.035$). Secondary outcomes of episode-free days, rate of respiratory tract illness, and rate of ED or urgent care visits did not differ between the vitamin D deficient and sufficient groups.

The effect of vitamin D deficiency on the treatment of asthma has also been investigated. In the CAMP trial, the effect of vitamin D and treatment with budesonide on pre-bronchodilator FEV1, bronchodilator response to inhaled β -agonist (BDR), and provocative concentration of methacholine producing a 20% decline in FEV1 (PC20) over the first 8–12 months of the study was evaluated.¹⁴ This duration was chosen, since the maximum effect of inhaled corticosteroid (ICS) on BDR was observed at the first 12 months of the CAMP study. Treatment with ICS was associated with a significantly greater change in prebronchodilator FEV1 and FEV1 percent predicted in children with sufficient (>30 ng/mL) or insufficient (20–30 ng/mL) vitamin D compared to deficient (<20 ng/mL) vitamin D children (least squares regression, adjusted for age, race, sex, BMI, history of ED visit, and season when vitamin D was measured, $p=0.0072$ and $p=0.036$ respectively). Although the change in BDR decreased in both sufficient and insufficient vitamin D children and increased in vitamin D deficient children, the association was not significant. There was no significant association between the outcomes, vitamin D status, and placebo or nedocromil treatment arms. The authors concluded that sufficient

vitamin D level in conjunction with ICS is associated with improved lung function, indicating that vitamin D may enhance the anti-inflammatory effect of ICS in children with asthma. Similar results were reported in a cross-sectional study of adult patients with asthma.¹⁵ A significant correlation was shown between FEV1 and vitamin D concentration in 54 asthmatic patients ($p=0.02$, $r=0.8$) with a stronger association between ICS untreated patients compared to those who were treated with ICS.

Vitamin D concentration and the effect of corticosteroids on bone mineral density (BMD) in children with asthma have been investigated. Bone mineral accretion (BMA) and vitamin D status were evaluated in 780 children in the CAMP cohort.¹⁶ Boys with insufficient vitamin D had more than twice the decrease in BMA with exposure to more than two courses of oral corticosteroids per year compared to those with sufficient vitamin D status ($p<0.001$). This effect was associated with a risk of osteopenia but not fracture. The result suggests a possible means of minimizing the effect of corticosteroids on bone metabolism. In a randomized, double-blind study in adult patients with mild to moderate asthma, patients were randomly assigned to daily doses of mometasone furoate 400 μ g or 200 μ g, fluticasone propionate 500 μ g or montelukast 10 mg for 1 year.¹⁷ All patients had 25-OH-Vit D concentrations >15 ng/mL at baseline and continued a daily dose of 500 mg calcium + 400 IU vitamin D during the study. BMD was assessed at baseline, 6 months, and 1 year. No significant differences were reported among treatments for BMD.

As evidence suggests a protective effect of vitamin D for asthma exacerbations, the next step is to investigate whether vitamin D supplementation can improve asthma outcomes. Castro *et al.*¹⁸ evaluated vitamin D supplementation in adult patients on ICS with uncontrolled asthma and vitamin D concentrations <30 ng/mL. This study was the first prospective multicenter trial of vitamin D supplementation. It was a randomized, double-blind, parallel, placebo-controlled trial; 408 patients were assigned to either placebo or one dose of vitamin D₃ 100,000 IU followed by 4,000 IU/day for 28 weeks added to inhaled ciclesonide 320 μ g/day. The dose of ICS was decreased by 50% twice to 80 μ g/day if asthma was controlled. The primary end point was the time to the first asthma treatment failure, which was defined as a composite outcome of decline in lung function, use of systemic corticosteroid, healthcare use, and increase in use of β_2 -agonist. Eighty-two percent (157/201) of patients on vitamin D₃ supplement achieved a serum 25-OH-VitD concentration >30 ng/mL at 12 weeks, and it was maintained for the duration of the study. The mean serum 25-OH-VitD concentration remained <20 ng/mL in the placebo group. The rate of first treatment failure, overall treatment failure rate, first exacerbation, or overall exacerbation rate did not differ between the treatment groups during 28 weeks of the study. In an exploratory analysis, vitamin D responders (157 patients with 25-OH-VitD >30 ng/mL) had a significantly lower overall rate for asthma treatment failure and exacerbation compared to the placebo group. This finding suggests that a targeted 25-OH-VitD level may be necessary in future trials rather than a fixed dose of vitamin D for all participants. Several small studies of vitamin D supplementation have been conducted in children, but these studies did not have asthma exacerbation as a primary outcome or had enrolled patients with sufficient vitamin D in the study.^{19–22}

In summary, there is growing body of literature investigating the association between vitamin D and asthma in pediatric and adult patients. It is still not clear what the optimal vitamin D level is for asthma. It is difficult to interpret the results of observational or cross-sectional studies, since the level of vitamin D at the time of exacerbation or lack of asthma controls are not available. The strongest evidence for asthma control and vitamin D seems to be in the pediatric population. In light of recent literature, supplementation with vitamin D in children with insufficient levels seems reasonable. However, well-designed clinical trials are needed to investigate the sufficient level of vitamin D for immune function and vitamin D supplementation (including dose, delivery, and duration) for improvement of asthma outcome in children.

Author Disclosure Statement

No competing financial interests exist.

References

1. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med* 2013;369:1991–2000.
2. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–58.
3. Brehm JM. Vitamin D and asthma—life after VIDA? *Curr Allergy Asthma Rep* 2014;14:461.
4. Hollams EM, Hart PH, Holt BJ, et al. Vitamin D and atopy and asthma phenotypes in children: a longitudinal cohort study. *Eur Respir J* 2011;38:1320–1327.
5. van Oeffelen AA, Bekkers MB, Smit HA, et al. Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study. *Pediatr Allergy Immunol* 2011;22:784–793.
6. Hollams EM. Vitamin D and atopy and asthma phenotypes in children. *Curr Opin Allergy Clin Immunol* 2012;12:228–234.
7. Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. *Curr Opin Allergy Clin Immunol* 2012;12:179–185.
8. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 2010;125:995–1000.
9. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054–1063.
10. Brehm JM, Schuemann B, Fuhlbrigge AL, et al.; Childhood Asthma Management Program Research Group. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. *J Allergy Clin Immunol* 2010;126:52–58.
11. Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011; 365:1990–2001.
12. Beigelman A, Zeiger RS, Mauger D, et al.; Childhood Asthma Research and Education (CARE) Network of the National Heart, Lung, and Blood Institute. The association between vitamin D status and the rate of exacerbations requiring oral corticosteroids in preschool children with recurrent wheezing. *J Allergy Clin Immunol* 2014;133:1489–1492.
13. Raissy HH, Blake K. Management of wheezing in pre-school children. *Pediatr Allergy Immunol Pulmonol* 2012; 25:172–173.
14. Wu AC, Tantisira K, Li L, Fuhlbrigge AL, Weiss ST, Litonjua A; Childhood Asthma Management Program Research Group. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. *Am J Respir Crit Care Med* 2012;186:508–513.
15. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 2010;181: 699–704.
16. Tse SM, Kelly HW, Litonjua AA, Van Natta ML, Weiss ST, Tantisira KG; Childhood Asthma Management Program Research Group. Corticosteroid use and bone mineral accretion in children with asthma: effect modification by vitamin D. *J Allergy Clin Immunol* 2012;130:53–60.
17. Maspero J, Backer V, Yao R, Staudinger H, Teper A. Effects of mometasone, fluticasone, and montelukast on bone mineral density in adults with asthma. *J Allergy Clin Immunol Pract* 2013;1:649–655.
18. Castro M, King TS, Kunselman SJ, et al. VIDA effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. *JAMA* 2014;311:2083–2091.
19. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;91:1255–1260.
20. Rich-Edwards JW, Ganmaa D, Kleinman K, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. *Am J Clin Nutr* 2011;94:578–584.
21. Camargo Jr CA, Ganmaa D, Frazier AL, et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics* 2012;130: e561–567.
22. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol* 2011;127:1294–1296.

Address correspondence to:
Hengameh Raissy, PharmD
Department of Pediatrics
School of Medicine
University of New Mexico
Albuquerque, NM 87131-0001

E-mail: hraissy@salud.unm.edu

Received for publication September 9, 2014; accepted after revision November 11, 2014.