

Evidence for the Role of Inadequate Vitamin D in Asthma Severity Among Children

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Abstract: Asthma is the most common chronic pediatric medical condition in the United States and accounts for significant morbidity, particularly among minority and disadvantaged populations. Hypovitaminosis D is also highly prevalent throughout the developed world, and many of the risk factors for hypovitaminosis D and asthma are the same. Several recent observational studies have documented a correlation between asthma severity and vitamin D levels; however, there is no strong evidence for causality yet. Until trials of vitamin D supplementation among children with asthma are performed, the role of low levels of vitamin D in causing asthma morbidity will remain unclear.

Key Words: asthma, vitamin D

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Asthma is a public health epidemic, affecting more than 24.6 million people in the United States,¹ including approximately 7 million children younger than 18 years.² It is the most common chronic pediatric medical condition worldwide, with approximately 80% to 90% of cases diagnosed in children younger than 6 years.^{3,4} Its prevalence has increased dramatically since the early 1980s.¹ Each year, children with asthma in the United States make more than 600,000 emergency department visits for acute exacerbations, account for more than 150,000 hospitalizations, and miss nearly 10.5 million school days.¹ Risk factors for childhood asthma include male sex,⁵ African American race,⁶ atopy,⁷ a family history of asthma and/or atopy,⁸ sensitivity to perennial and seasonal allergens,⁹ viral respiratory infections,¹⁰ endotoxin exposure,¹¹ exposure to particulate matter,¹² and active smoking.^{13,14} Asthma is also distinguished by dramatic racial and ethnic disparities in severity. According to recent statistics from the Centers for Disease Control and Prevention, for example, when compared with their white counterparts, African Americans have a 3.3 times higher rate of emergency department visits for asthma exacerbations, a 2.2 times higher rate of hospitalizations, and a 1.9 times higher rate of death from the disease.¹

Vitamin D has long been known for its role in calcium metabolism and bone health. However, emerging evidence suggests that it may play important roles in modulating a wide range of chronic inflammatory conditions and infections such as asthma, Crohn's disease, tuberculosis, type 1 diabetes, multiple sclerosis, and various types of cancers.^{3,15} Vitamin D is both a nutrient and

a steroid hormone. Unlike most nutrients, it only occurs naturally in a select number of foods, namely, oily fish, fish liver oil, and egg yolk.¹⁶ The remainder is obtained from supplemented dairy products or through activation of precursors in the skin when they are exposed to UV-B rays from sunlight. Through a photosynthetic mechanism, 7-dehydrocholesterol is converted to pre-vitamin D₃, which undergoes isomerization and activation in the liver and kidneys. Of note, immune cells and lung epithelial cells both express high levels of 1 α -hydroxylase, which converts inactive 25(OH)D to the active form of vitamin D, 1,25(OH)D.³ The inactive 25(OH)D form is routinely measured in the serum as an indirect marker of body stores.

Hypovitaminosis D is highly prevalent in westernized countries despite efforts to fortify dairy products and cereal. Data from the 2001 to 2004 National Health and Nutrition Examination Survey estimate that approximately 9% of children (or 7.6 million US children and adolescents) are vitamin D deficient (serum 25[OH]D level, <15 ng/mL) and 61% (or 50.8 million US children and adolescents) are vitamin D insufficient (serum 25[OH]D level, 15–29 ng/mL).¹⁷ In another study of National Health and Nutrition Examination Survey data, Mansbach et al.¹⁸ found that 69% of all children aged 6 to 11 years had serum 25(OH)D levels that were lower than 30 ng/mL, including 92% of non-Hispanic black children and 80% of Hispanic children aged 6 to 11 years. Low levels of vitamin D seem to be most common in older, African American females who drink milk less than once per week or spend more than 4 hours daily on sedentary indoor activities, such as playing video games, watching television, and using the computer. Furthermore, vitamin D production is decreased during the months of November through March because of insufficient UV-B rays, additional clothing worn, and less time spent outdoors.^{18,19}

Although vitamin D insufficiency and deficiency (most commonly defined as ≤ 30 and ≤ 20 ng/mL of circulating serum 25[OH]D, respectively) are common among children, many of the same risk factors associated with hypovitaminosis D (such as African American race and obesity) are associated with pediatric asthma.²⁰ As Litonjua and Weiss¹⁹ point out in a recent review, countries furthest from the equator, such as Australia and New Zealand, have the highest rates of both asthma and vitamin D deficiency. People in westernized countries are also prone to vitamin D deficiency and asthma because they spend most of their time indoors. According to the Environmental Protection Agency's National Human Activity Pattern Survey, 95% of Americans work indoors and therefore spend only 10% of available daylight outside.²⁰

Vitamin D deficiency tends to affect impoverished, obese, African American children who lack sufficient sun exposure in industrialized countries.³ Children with asthma spend less time outdoors compared with their healthy counterparts, presumably because seasonal allergies and weather changes can be significant triggers for asthma attacks. As such, young children with asthma may tend to have less exposure to UV-B rays necessary to allow for cutaneous vitamin D production, even in sun-laden areas such as Costa Rica.²¹ Children with asthma also tend to

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drink less milk, which puts them at risk for vitamin D deficiency.²² A small, recent, case-control study by Freisztat et al.²³ examined the rates of vitamin D deficiency and insufficiency among African American children and young adults aged 6 to 20 years residing in Washington, DC (located at 38°55'N). In this series, a total of 86% of patients with asthma were vitamin insufficient, and the adjusted odds ratio of 25(OH)D deficiency was 20 (95% confidence interval [CI], 1.4–272), whereas the adjusted odds ratio of 25(OH)D insufficiency was 42 (95% CI, 4.4–399).

Several recent observational studies also suggest that there may be a correlation between asthma severity and vitamin D levels among children with asthma. Unfortunately, any role for vitamin D levels in determining asthma severity in children is largely suggested by studies of association without strong evidence for causality. Until well-conducted and convincing trials of vitamin D supplementation among children with asthma are performed, the role of hypovitaminosis D in causing asthma morbidity will remain unclear. Studies of the association between vitamin D and asthma severity among minority children in northern latitudes may be further hampered by their high prevalence of vitamin D insufficiency. Because so many children have such low levels, any relationship between increasing levels of 25(OH)D and decreasing measures of asthma-related morbidity may seem blunted.

Brehm et al.²¹ recently conducted a cross-sectional observational study of 616 Costa Rican children between the ages of 6 and 14 years to assess the association between vitamin D exposure and asthma severity in a sun-replete developing area. Their study was remarkable among recently published studies in that only 28% of children with asthma were vitamin D insufficient (serum 25[OH]D levels, ≤ 30 ng/mL). In this cohort, rising serum levels of 25(OH)D were associated with lower markers of atopy (total serum IgE and peripheral eosinophil counts), fewer positive methacholine challenges (a marker of airway hyperresponsiveness), less frequent use of inhaled corticosteroids in the previous year, and fewer asthma-related hospitalizations in the previous year.²¹ Of note, however, there was no association in this study between vitamin D levels and unscheduled visits for asthma care. In a later observational cohort study nested within the multicenter Childhood Asthma Management Program study, Brehm et al.²⁴ observed 1024 largely nonminority and suburban children with mild to moderate persistent asthma in the United States for 4 years. Consistent with their Costa Rican counterparts, the rate of vitamin D insufficiency in this group was relatively low (35.0%). Insufficiency was most common among older, obese, African American participants and among those tested during the winter and spring. In this cohort, vitamin D insufficiency was significantly associated with an elevated adjusted odds ratio of any asthma-related emergency department visit or hospital admission (adjusted odds ratio, 1.5; 95% CI, 1.1–1.9).²⁴

In a recent cross-sectional study of 100 US children with asthma, aged 0 to 18 years, Searing et al.² looked at a wide range of markers of atopy and asthma control related to serum levels of 25(OH)D. Overall, 53.0% of the sample had insufficient serum 25(OH)D levels (again defined as <30 ng/mL), a prevalence of insufficiency much higher than in either of the reports from Brehm et al. Nonetheless, the investigators demonstrated significant associations between increasing vitamin D levels and lower serum IgE, fewer positive skin-prick tests to perennial aeroallergens, improved spirometric measures, and less use of inhaled and enteral steroids for asthma control. Finally, in a very recent cross-sectional observational study of 75 Italian children with asthma, aged 5 to 11 years, Chinellato et al.²⁵ documented

significant and positive correlations between serum 25(OH)D levels and improved spirometric measurements of airway obstruction and a common measure of asthma control (the Childhood Asthma Control Test). These findings were apparent despite a prevalence of vitamin D insufficiency of 90.6%.

Several authors have speculated that the mechanism underlying any association between vitamin D deficiency and asthma morbidity most likely involves an increased risk of respiratory infections,²² which are a frequent cause of asthma exacerbations and subsequent hospitalizations.²¹ Similarly, early viral respiratory infections have been associated with an increased predisposition to asthma.²⁶ Although patients with asthma are not at a higher risk for infection, they are at risk for more serious infections triggering asthma exacerbations.¹⁰ In a recent randomized placebo-controlled trial conducted by Urashima et al.,²⁷ school-aged Japanese children receiving 1200 IU of vitamin D₃ daily had fewer influenza A infections. Interestingly, among the subgroup of children with asthma who received supplementation in this study, the relative risk of any asthma exacerbation was significantly lower than in the control group.

Mechanistically, a plausible role for the antiviral effect of vitamin D involves cathelicidin, specifically, hCAP-18, the human version of a family of mammalian polypeptides found in lysosomes in macrophages and polymorphonuclear leukocytes. Human cathelicidin has several antimicrobial effects, including microbial killing within phagocytic vacuoles and attraction of neutrophils and monocytes. It also has vitamin D-dependent up-regulatory mechanism. In brief, microbial exposure to the toll-like receptors on macrophages upregulates genes coding for the vitamin D receptor and for 1α -hydroxylase. The resulting increased levels of 1,25(OH)D then promote the production of hCAP-18.^{28–31}

According to the Institute of Medicine's most recent report in 2010, the recommended dietary allowance of vitamin D increased from 400 to 600 IU for children older than 1 year to compensate for the high prevalence of vitamin D deficiency among this age group in the United States.³² Nevertheless, only 1 of 3 children is on vitamin D supplementation,¹⁸ and the current recommended doses still may not be enough. Prospective studies of vitamin D supplementation are needed to elucidate the true role of hypovitaminosis D in asthma severity.

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