Childhood asthma may be a consequence of vitamin D deficiency

Augusto A. Litonjua, MD, MPH
Channing Laboratory and Pulmonary and Critical Care Division, Department of Medicine, Brigham and Women's Hospital; Harvard Medical School, Boston, Massachusetts

Abstract

Purpose of Review—Vitamin D deficiency has been rediscovered as a public health problem worldwide. It has been postulated that vitamin D deficiency may explain a portion of the asthma epidemic. The purpose of this review is to present the evidence for a role of vitamin D in asthma.

Recent Findings—Both animal models and studies in human fetal tissues show that vitamin D plays a role in fetal lung growth and maturation. Epidemiologic studies have also suggested that higher prenatal vitamin D intakes have a protective role against wheezing illnesses in young children. Vitamin D may protect against wheezing illnesses through its role in upregulating antimicrobial proteins or through its multiple immune effects. In addition, vitamin D may play a therapeutic role in steroid resistant asthmatics, and lower vitamin D levels have recently been associated with higher risks for asthma exacerbations.

Summary—Improving vitamin D status holds promise in primary prevention of asthma, in decreasing exacerbations of disease, and in treating steroid resistance. However, the appropriate level of circulating vitamin D for optimal immune functioning remains unclear. Because vitamin D deficiency is prevalent even in sun-replete areas, clinical trials are needed to definitively answer questions about the role of vitamin D in asthma.

Keywords
asthma; vitamin D; allergies; sun exposure; wheeze

Introduction

Asthma and related allergic diseases are substantial public health problems world wide[1,2]. Asthma remains the most common chronic disease of childhood in the world[2,3], and is one of the leading causes of morbidity in children. Asthma prevalence is highest in Westernized, industrialized countries[1], and we have recently proposed that vitamin D deficiency may explain some part of this pattern[4]. This topic has not been reviewed in this journal previously, and this review will examine evidence for the potential roles of vitamin D in the inception and expression of asthma.

Epidemiology of Vitamin D Deficiency

Vitamin D deficiency was thought to be eradicated with the fortification of foods and the apparent disappearance of rickets. However, vitamin D deficiency has been ‘rediscovered’ and associations with many disorders are being recognized[5*]. Vitamin D does not naturally occur in foods that humans eat, except in oily fish and fish liver oil, egg yolk, and offal such as liver [6]. Currently, most vitamin D is obtained from fortified foods and from supplements. From
an evolutionary standpoint, humans do not require vitamin D in the food supply because we have a photosynthetic mechanism in the skin. 7-Dehydrocholesterol (7-DHC) is distributed in the skin. After exposure to sunlight, 7-DHC is converted to previtamin D$_3$, which is then transformed to vitamin D$_3$ by a thermally induced isomerization. Vitamin D$_3$ then undergoes hydroxylation in the liver to 25(OH)D and then in the kidney to its biologically active form 1,25-dihydroxyvitamin D$_3$ (1,25[OH]$_2$D). Serum 25(OH)D is the major circulating metabolite of vitamin D, reflects input from cutaneous synthesis and dietary intake, and measurement of levels is the standard measure of vitamin D status. The determinants of vitamin D status include exposure to the sun and time spent outdoors[7,8], diet and supplement use[8], latitude, season, age, skin color, and skin coverage (i.e. clothing and sunblock use) [9]. Evaluations of most relations between vitamin D and health and various disorders lead to the conclusion that a desirable (or sufficient) circulating vitamin D level (measured as 25 hydroxyvitamin D, 25(OH)D) is at least 30 to 40 ng/ml (75 to 100 nmol/L)[5,10,11]. Levels of 25(OH)D between 20 and 30 ng/ml (50 and 75 nmol/L) are considered relative insufficiency. There are suggestions that levels even higher than 40 ng/ml (100nmol/L) may be necessary for optimal immune functioning and overall health[12,13*], but further studies are needed.

Vitamin D deficiency has been documented in many populations worldwide[14,15], including children. Vitamin D deficiency has occurred despite fortification of foods in some Westernized countries and despite intake of multivitamins containing vitamin D, and in areas of the world that are considered sun-replete. This suggests that as countries adopt a western lifestyle, there is shift from outdoor activities to more time spent indoors. For example, it is estimated that in the US alone, Americans spend an average of 93% of their time indoors[16]. Relevant to the inception of asthma in young children, pregnant and lactating mothers and their neonates are at especially high risk for vitamin D deficiency[17-20]. Furthermore, it has recently been documented that 50% of mothers and 65% of their newborn infants from an inner city hospital were vitamin D deficient, with levels <12 ng/ml (or <30 nmol/L)[21*], despite the fact that most mothers were taking their prenatal vitamins. This analysis also showed a strong positive correlation between maternal and newborn plasma levels, providing further evidence that infant vitamin D status is dependent on maternal vitamin D status. This is an important fact when considering primary prevention of disorders such as asthma that may have their roots in the prenatal period.

**Is vitamin D involved in asthma?**

To date, only a handful of studies have directly evaluated the role of vitamin D in asthma. However, there is a growing literature that indirectly relates vitamin D with mechanisms in asthma. These studies will be summarized below.

**Genetics**

Initial direct evidence implicating vitamin D in asthma and allergy development came from human genetic association studies. Significant associations between polymorphisms in the Vitamin D receptor (VDR) gene with asthma were reported concurrently in two studies of North American Subjects using family-based study designs[22,23]. However, two subsequent German studies did not find significant associations[24,25], although both these studies had fewer subjects than the previous ones. More recently, the same German group found that genetic variation in genes, other than VDR, involved in vitamin D metabolic and signaling pathways were preferentially transmitted to asthmatic children[26].

Genetic studies have also been performed in animal models and human tissues in vitro. Studies in mouse models from one research group have shown that VDR knockout mice do not develop experimental asthma[27] and that expression of VDR is necessary for induction of lung inflammation[28]. A few studies have been conducted with human tissues. Using RT-PCR and
Western blot techniques, Bossé et al recently found that VDR is present in human bronchial smooth muscle cells[29*]. More importantly, they demonstrated that the expression of many genes is regulated in these cells following 1α,25(OH)2D3 stimulation, including genes previously implicated in asthma predisposition and pathogenesis. Analyses of expression data permitted the elaboration of different biological scenarios by which VDR may be associated with asthma, including smooth muscle cell contraction, inflammation, as well as glucocorticoid and prostaglandin regulation. More comprehensive analyses indicated a network of up-regulated genes with functional importance for cellular movement, cellular growth and proliferation, and cell death, which likely plays a role in airway remodeling that occurs in some asthmatics.

Thus, the genetics of vitamin D in asthma is likely to be highly complex and more studies investigating genes in the metabolic pathway and gene-by-vitamin D level interaction analyses are needed.

Infections

The role of infections in the inception of asthma continues to be debated. It has been hypothesized that as family sizes have decreased, exposure to infections and microbial products have decreased leading to an increase in asthma and allergies[30,31]. On the other hand, respiratory viruses are potent triggers of asthma exacerbations and early life respiratory viral infections have been associated with the development of asthma[32]. While it appears that asthmatics are not at increased risk for developing infections, they are at higher risk for more severe symptoms with these infections[33]. Thus, host factors likely determine who develops asthma as a consequence of viral infections. Vitamin D status is one such factor that can mediate this risk. Vitamin D induces the production of the antimicrobial polypeptide, cathelicidin[34], which has both bacterial and anti-viral effects[35,36]. Supplementation with vitamin D was shown to decrease the incidence of cold or influenza symptoms in a clinical trial of 208 black women[37*]. A study from the third National Health and Nutrition Examination showed that individuals with lower circulating 25(OH)D levels had higher risks for recent upper respiratory tract infection symptoms[38]. However, whether the administration of vitamin D can prevent the development of asthma and/or asthma exacerbations through a decrease in infections remains to be tested.

Immune system effects

Vitamin D receptors (VDR)[39,40] and vitamin D metabolic enzymes[14,41] have been identified in cells of the immune system, such as T[42], activated B cells[43], and dendritic cells[44]. In murine models, evidence exists that vitamin D may induce a shift in the balance between Th1 and Th2-type cytokines toward Th2 dominance[45,46]. Reduced secretion of Th1 cytokines IL-2 and IFN-γ[46-48] and an increase in the Th2 cytokine IL4[49,50] have been observed in several experiments after treatment with 1,24(OH)2D. However, Matheu et al[46] have shown that vitamin D has dual effects of both enhancing and suppressing allergic Th2 responses in a murine model of pulmonary eosinophilic inflammation. Topilski et al[51], in an in vivo murine model of Th2 dependent asthma, showed that vitamin D has profound effects in downregulating inflammatory responses and reduced IL-4 production in bronchoalveolar lavage fluid. It is difficult to reconcile these effects in these different models, but it may have to do with the timing and chronicity of vitamin D administration relative to sensitization. Consistent with this, a recent study showed that mice who were exposed to UVB radiation (a single erythemal dose) prior to intraperitoneal sensitization showed attenuated airway responsiveness and cellular responses in the airways to allergens[52]. In human cells, vitamin D also has the ability to inhibit both Th1- and Th2-type responses. Pichler et al.[53, 54] showed that in CD4+ as well as CD8+ human cord blood cells, vitamin D inhibits not only
IL-12-generated IFN-γ production, but also suppresses IL-4, and IL-4-induced expression of IL-13.

Aside from the effects of vitamin D on Th1 and Th2 responses, there is a growing recognition that it promotes the induction of T-reg cells[55-57]. The characteristic features of Treg cells include the expression of potentially inhibitory cytokines (IL10 and TGFβ), and the ability to potently inhibit antigen-specific T cell activation[58,59]. These effects of vitamin D on the immune system underlie the regulator role of vitamin D and are thought to be orchestrated by an array of intracellular signaling pathways in lymphocytes and antigen-presenting cells of which IL10 and TGFβ are the most important (reviewed in Griffin et al.[60]). These pathways lead to either over- or under-expression of genes. For example, vitamin D has been shown to modify levels or function of NF-κB proteins such as Rel-B and c-Rel.[61-63] Finally, vitamin D-dependent binding of vitamin D receptor (VDR) complexes directly to promoter regions of activation-induced genes in T lymphocytes has been shown[64]. Directly relevant to asthma, there is evidence that vitamin D may have a therapeutic role in steroid-resistance by enhancing responsiveness to glucocorticoids for induction of IL-10. Yxstrakis et al[65] obtained peripheral blood CD4+ T cells from steroid sensitive and steroid resistant asthmatics and found that administration of vitamin D was shown to reverse steroid-resistance through induction of IL-10 secreting T-reg cells. A subsequent study showed that in combination with fluticasone, 1α,25(OH)2D3 modulates human airway smooth muscle secretion of pro-inflammatory chemokines[66**]. An additional role of vitamin D in allergic asthma may be to potentiate the effects of allergen immunotherapy. In a mouse model of allergic asthma, co-administration of 1α,25(OH)2D3 with allergen immunotherapy significantly inhibited airway hyperresponsiveness and potentiated the reduction of OVA-specific IgE levels, airway eosinophilia, and Th2 cytokines[67**].

**Effects on lung development and lung function**

Lung development begins in utero and continues through the first few years of life (reviewed in Burri[68]). At the end of fetal lung development, the alveolar epithelium undergoes abrupt differentiation as part of the preparation for gas exchange after birth. Fetal pulmonary maturation includes the differentiation of type II pneumocytes, with progressive disappearance of glycogen and the start of surfactant synthesis. Premature birth before adequate surfactant production has been established, results in the respiratory distress syndrome. Nguyen and coworkers, through a series of studies in fetal rat lung, have identified the type II alveolar cells as a target for 1,25(OH)2D3 action, and have shown that vitamin D is important in lung maturation and surfactant production[69-73]. In humans, the effect of vitamin D on surfactant production has been confirmed[74], although the mechanisms appear to be more complex than in the rat[75].

Aside from effects on type II pneumocytes and surfactant production, vitamin D also appears to have effects on lung growth and development. Gaultier et al[76] studied lung mechanics in 50-day old rats born to mothers deprived of dietary vitamin D and reported significantly decreased lung compliance compared with rats born to mothers whose diet was supplemented with vitamin D, suggesting that disturbances in lung growth occurred in the vitamin D deficient rats. In humans, vitamin D also has been shown to play a role in the developing lung. Early studies used the presence of calbindin, a vitamin D dependent calcium binding protein, as a molecular marker of 1,25(OH)2D3 action in tissues. Among many other tissues, Brun et al[77] reported high levels of calbindin in human fetal lung tissue at 14-32 weeks of gestation, suggesting that vitamin D plays a role in fetal lung development, as early as 14 weeks. Lunghi and colleagues[78] obtained normal human fetal (16 weeks gestation) lung fibroblasts and reported that in the presence of vitamin D, pyruvate kinase activity and lactate production of the cells increased. Other findings included a decrease in cell number and DNA synthesis in...
the vitamin D exposed cells compared with control cells. Subsequently, they showed that the vitamin D receptor was present in these human fetal fibroblasts[79] and confirmed their original findings in fetal lung fibroblasts in a subsequent study on senescent human lung fibroblasts [80]. However, no study to date has examined the effects of maternal vitamin D status in pregnancy (and thus, fetal vitamin D status) on early life lung function.

A recent study has reported associations between vitamin D and lung function in adults. Black and Scragg analyzed cross-sectional data from the Third National Health and Nutrition Examination Survey and found that serum 25-OH vitamin D was positively associated with FEV\textsubscript{1} and FVC in the US general population[81].

**Vitamin D and asthma development**

Based on the effects of vitamin D on the developing immune system and the lung, it is intriguing to speculate on whether an adequate vitamin D status might prevent the development of asthma in children. We recently reported protective effects of higher maternal dietary vitamin D intakes in pregnancy on wheezing phenotypes in young children in two separate cohorts[82**,83**]. The first analysis was conducted in 1194 mother-child pairs from Boston, MA, and showed that 3-yr old children born to mothers who had intakes of vitamin D in the highest quartile during pregnancy had a 62% reduction in their risk of recurrent wheeze (adjusted OR=0.38, 95% CI=0.22, 0.65). In a second analysis on 1212 mother-child pairs from Aberdeen, Scotland, we showed that children born to mothers who had vitamin D intakes in the highest quintile had a 67% reduction in their risk of persistent wheeze at age 5 years (adjusted OR=0.33, 95% CI=0.11, 0.98). A third study from Finland on 1669 mother-child pairs has also shown a protective effect of higher maternal vitamin D intake on asthma in 5-yr old children[84**]. Additionally, this last study also found a protective effect of higher maternal vitamin D on allergic rhinitis. These studies are limited by the fact that vitamin D intake was calculated from food frequency questionnaires (thus, no direct measure of vitamin D status in the mothers) and may be confounded by diet quality. However, all studies adjusted for total energy intake and for other nutrients associated with healthy diets.

Two other studies showed an adverse effect of vitamin D on asthma and allergies. A birth cohort from Northern Finland has shown that vitamin D supplementation in the first year of life increased the risk for asthma and atopy at 31 years of age[85]. However, this study did not assess maternal prenatal vitamin D status or intake, and did not assess childhood asthma or atopy. A second study measured circulating vitamin D levels in pregnant women and reported that higher circulating vitamin D levels in pregnant women were associated with increased risks for eczema at 9 months and asthma at 9 years[86]. However, results were reported only in univariate models without adjustment for potential confounders, and there was significant loss to follow-up (61.8%) in the cohort, especially at 9 years. Thus, the question of whether adequate vitamin D status can prevent asthma remains unanswered. The issue of prenatal vitamin D supplementation in preventing asthma in children is being addressed by an ongoing clinical trial in the US.

**Vitamin D and asthma exacerbations**

In 616 Costa Rican children with asthma aged 6-14 years, we found that 28% of the children had insufficient vitamin D levels[87**]. This was consistent with other studies that have found a high prevalence of vitamin D insufficiency in sun-rich environments. In adjusted logistic regression models, a log\textsubscript{10}–unit increase in vitamin D levels was associated with reduced odds of any hospitalization for asthma in the previous year (odds ratio [OR]=0.05, 95% confidence interval [CI]=0.004–0.71, P=0.03) and any use of anti-inflammatory medications in the previous year (OR=0.18, 95% CI=0.05–0.67, P=0.01). In addition, in adjusted linear regression
models, vitamin D levels were significantly and inversely associated with total IgE and eosinophil count.

**Conclusions**

As humans live more prosperous lives, we spend more time indoors exacerbating the problem of vitamin D deficiency. Vitamin D has many actions aside from its bone maintenance effects. Of relevance to asthma, vitamin D has effects on the immune system and on lung development and function. Preliminary epidemiologic studies hint at a possible role of vitamin D in asthma development and in decreasing exacerbations. However, because of potential confounding factors, well-designed clinical trials are needed to answer these questions. Additionally, more studies are needed to determine the proper circulating level of vitamin D for optimal immune function.

**References**

*13. Holick MF. Circulating vitamin D(3) and 25-hydroxyvitamin D in humans: An important tool to define adequate nutritional vitamin D status. J Steroid Biochem Mol Biol 2007;103:631–634. [PubMed: 17218096] This study investigated the relationship between circulating vitamin D(3) and its metabolic product - 25(OH)D(3) - in 2 separate populations By comparing these substances, this study suggested that levels of 25(OH)D(3) that define optimal nutritional vitamin D status is likely higher than currently thought.


29. Bosse Y, Maghni K, Hudson TJ. 1alpha,25-dihydroxy-vitamin D3 stimulation of bronchial smooth muscle cells induces autocrine, contractility, and remodeling processes. Physiol Genomics 2007;29:161–168. [PubMed: 17213369] This study confirms that vitamin D receptors are present in human lung tissue. The authors also show that after vitamin D stimulation, a range of genes are expressed in these bronchial smooth muscle cells that are involved in airway remodeling.


35. Grant WB. Hypothesis--ultraviolet-B irradiance and vitamin D reduce the risk of viral infections and thus their sequelae, including autoimmune diseases and some cancers. Photochem Photobiol 2008;84:356–365. [PubMed: 18179620]


60. Griffin MD, Xing N, Kumar R. Vitamin D and its analogs as regulators of immune activation and antigen presentation. Annu Rev Nutr 2003;23


67. Taher YA, van Esch BC, Hofman GA, Henricks PA, van Oosterhout AJ. 1alpha,25-dihydroxyvitamin D3 potentiates the beneficial effects of allergen immunotherapy in a mouse model of allergic asthma: role for IL-10 and TGF-beta. J Immunol 2008;180:5211–5221. [PubMed: 18390702] In this mouse model of allergic asthma, this study showed that when vitamin D is given concurrently with allergen immunotherapy, it potentiated the beneficial effects of immunotherapy Most importantly, the co-administration of vitamin D with immunotherapy inhibited airway hyperresponsiveness, which immunotherapy alone did not inhibit.


**84. Erkkola M, Kaila M, Nwaru B, Kronberg-Kippila C, Ahonen S, Nevalainen J, Veijola R, Pekkanen J, Ilonen J, Simell O, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year old children. Clin & Exp Allergy. 2009 In Press. The first two articles, published at the same time, were the first to show that higher maternal vitamin D intakes in pregnancy was associated with decreased risks for wheeze in the mothers' offspring The third study is a recent study from another cohort that showed that higher maternal vitamin D intakes in pregnancy decreased the risks for asthma in 5-yr old children Additionally, there was also an effect on allergic rhinitis No study directly measured maternal vitamin D status, however.


Brehm JM, Celedón JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Laskey D, Sylvia JS, Hollis BW, Weiss ST, et al. Serum Vitamin D Levels and Markers of Severity of Childhood Asthma in Costa Rica. Am J Resp Crit Care Med. 2009 In Press. This study is the first to show a relationship between vitamin D levels and risk for asthma exacerbation in a cohort of asthmatics. Additionally, this article confirmed that even in an area of the world that is near the equator (latitude 10° N), vitamin D deficiency exists.