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Vitamin D Deficiency as a risk factor for childhood allergic disease and asthma

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Abstract

Purpose of Review—Over the past 2 years, the number of studies relating vitamin D deficiency and asthma and allergies has increased significantly. The purpose of this review is to update the last review in this journal and examine the evidence of the relationship between vitamin D deficiency and childhood asthma and allergies.

Recent Findings—In the past 2 years since the last review, there have been many studies, both cross-sectional and prospective, that have investigated the effects of vitamin D on the inception and severity of asthma and allergies. Most, but not all, studies have shown that low vitamin D levels increase the risk for asthma and allergies, but a few suggest an increased risk with high levels. Results from small trials of short duration suggest that vitamin D supplementation decreases severity of eczema and decreases the risk for asthma exacerbations.

Summary—Data that vitamin D deficiency results in increased risks for asthma and allergies continues to accumulate. However, the optimal level of vitamin D that decrease both the risk for development and severity of these disorders remains elusive. Results of ongoing clinical trials of vitamin D supplementation will be needed before recommendations can be firmly established.

Keywords

asthma; vitamin D; allergies; wheeze

Introduction

Asthma and allergies are common chronic diseases in industrialized countries(1–3). By the year 2025, as more communities adopt a westernized lifestyle and become urbanized, it is expected that there will be 400 million people worldwide with asthma. In the United States, recent reports from national surveys show that the prevalence of asthma continues to rise in both children and adults, and in all racial and ethnic groups(4, 5). Among children (<18 yrs old), the prevalence of asthma increased from 8.7% in 2001 to 9.6% in 2009(4). The highest rates were observed among poor children, non-Hispanic Black children, and the northeast.

While data is not as detailed as that for asthma, other allergic disorders have also shown increases. For eczema, wide variations in prevalence have been documented in different parts of the world, with the largest rates in developed countries(6). In the International Study of Asthma and Allergies in Childhood (ISAAC), eczema prevalence was seen to increase in

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developing countries over a 5–10 year period between surveys(7). Similar patterns have been seen for allergic rhinitis(8).

While many potential reasons could account for the pattern of increased allergic disease in developed countries, vitamin D deficiency has been proposed as a risk factor that could explain a significant proportion of these increases. Vitamin D deficiency has been documented in many countries worldwide, even in areas that are considered sun-replete(9–11). This topic has been reviewed in this journal(12), and this review will examine the recent studies, published between 2009 and 2011, that have investigated the role of vitamin D in childhood asthma and allergies.

Vitamin D Deficiency in Asthma and Allergy Development

Potential mechanisms of how vitamin D can affect the risk of developing asthma and allergies have been reviewed recently (summarized in Figure 1)(12, 13). Briefly, vitamin D has both in-utero and post-natal effects on lung development and immune system development and function. In the in utero period, vitamin D appears to play a role in fetal lung development, and recent findings support this. Zosky and colleagues(14*) studied the effects of vitamin D deficiency in a murine model. Offspring of vitamin D deficient mice had decreased lung volumes compared to offspring of vitamin D replete mice, although there was no difference in histologic lung architecture. This study adds to the literature that vitamin D deficiency in utero affects lung development(15*). Vitamin D also appears to affect in utero immune system development that begins to exert its effects in early life. A recent study investigated effects of vitamin D levels in cord blood on immune function parameters. Chi et al(16*), using data from the Urban Environment and Childhood Asthma study, showed that cord blood vitamin D levels were inversely associated with the proportion of $CD25^{+}$, $CD25^{Bright}$, and $CD25^{+}$ FoxP3 T-regulatory cells. While the clinical consequence of this inverse association remains unclear, it supports the notion that in utero vitamin D levels affects immune development and may influence immune regulation early in life.

Post-natally, vitamin D may affect asthma and allergy development in several ways (Figure 1)(12, 13). Adequate vitamin D status may improve handling of respiratory infections early in life by upregulating the production of antimicrobial proteins, such as cathelicidin and beta defensins(17), dampening the inflammation associated with viral respiratory infections leading to a decrease in the sequelae of these viral infections. Additionally, adequate vitamin D status in the postnatal period likely continues to affect lung development and immune system functioning.

Given the in-utero effects of vitamin D, it is possible that the risk for asthma in children could be affected by maternal vitamin D status during pregnancy. A cohort study of 763 Japanese mother-infant pairs found that the risk for wheezing (adjusted OR (95%CI) = 0.64 (0.43–0.97) and eczema (adjusted OR (95%CI) = 0.63 (0.41–0.98) were significantly decreased among children 16–24 months of age whose mothers had higher vitamin D intakes in pregnancy(18). The results of this study are consistent with previous studies that assessed maternal intakes of vitamin D during pregnancy via a food frequency questionnaire (FFQ) (reviewed in Litonjua(12)). As with the previous studies, this study is limited by the lack of direct measurement of vitamin D levels.

Three recent studies have tried to address the limitations of the previous epidemiologic studies by directly measuring vitamin D status. These studies measured 25-hydroxyvitamin D_3 (25OHD), the circulating metabolite that defines vitamin D status. The first study addressed the effect of maternal 25OHD levels in pregnancy and the risk for lower respiratory tract infections, wheezing, and asthma in offspring. Morales et al(19*)

investigated 1724 children from a population-based cohort from 4 areas in Spain. They showed that maternal 25OHD levels (median 73.75 nmol/L or 29.5 ng/ml) were inversely associated with respiratory infections in children at 1 year of age, but not with wheezing at 1 yr or 4 yrs, or asthma between 4to 6 years. Since maternal vitamin D levels in pregnancy correlate with cord blood levels, other studies measured cord blood levels of vitamin D and the risk for subsequent outcomes in children. Camargo and colleagues measured 25OHD in 922 newborns participating in a population-based birth cohort, the New Zealand Asthma and Allergy Cohort Study(20*). While cord blood 25OHD levels (median 44 nmol/L or 17.6 ng/ml) were found to be inversely associated with wheezing illnesses by age 5 yrs, there was no association with incident asthma at age 5 yrs. These findings were consistent with the study by Morales et al, and a closer examination of the figures from these articles suggest a trend toward decreased asthma with higher vitamin D levels. Another study assessed 219 participants in the Tucson Infant Immune Study(21) and did not find an association between cord blood levels and asthma and allergic rhinitis by age 5 yrs. However, this study reported that both low (<50 nmol/L or 20 ng/ml) and high (≥100 nmol/L or 40 ng/ml) 25OHD levels were associated with higher total and inhalant IgE levels, but only higher levels were associated with skin prick testing. While these studies move the field forward, they are still limited by only one measure of vitamin D status and the time interval between measurement of vitamin D levels and the outcome, since vitamin D levels are known to fluctuate in populations. The discrepancies between these studies that have measured vitamin D status and the studies that have estimated vitamin D intake from FFQs likely lie in the fact that vitamin D levels reflect current status while estimates of intake from FFQs reflect more chronic intakes(22). Additionally, no objective markers of asthma (i.e. bronchial hyperresponsiveness or bronchodilator response) were obtained. Nevertheless, the finding that higher levels of cord blood vitamin D levels lead to higher risks for allergen sensitization should give pause to supplementation with high doses of vitamin D, until these findings can be verified or refuted by ongoing clinical trials.

Other studies have investigated the association between vitamin D and asthma and allergies in the post-partum period. Several case-control studies have been performed in African-American(23), Qatari(24), and Iranian(25) children, all showing that the prevalence of vitamin D deficiency is greater among asthmatic children than in controls. Two studies have used data from the National Health and Nutrition Examination Surveys (NHANES). In one analysis of 3136 children and adolescents, allergic sensitization to 11 of 17 allergens was more common in those with vitamin D deficiency (<37.5 nmol/L or 15 ng/ml) after multivariable adjustment. Sensitization included food allergens (peanut and shrimp), indoor and perennial allergens (dog, cockroach, Alternaria sp), and pollen (ryegrass, ragweed, Bermuda grass, oak, birch, and thistle)(26**). Another analysis of 6857 participants ≥6 yrs old showed that vitamin D levels were inversely associated with current wheeze and asthma(27), although the effects were stronger in older (>50 years) subjects. These studies are cross-sectional studies and are subject to potential confounding. Two cohort studies in children have attempted to perform longitudinal analyses in children. In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort of over 300 children, serum vitamin D concentrations at age 4 years were inversely associated with asthma at ages 4 to 8 years(28*). Curiously, vitamin D levels at 8 years were positively associated with asthma at the same age. Hollams et al(29*), in a cohort of over 600 Australian children, showed that higher vitamin D levels at age 6 were protective against the development of asthma, rhinoconjunctivitis, and atopy at age 14. These effects appeared to be stronger for boys than for girls. A small study of 123 Swedish children(30), whose vitamin D intake in the first year of life was quantified, showed increased risks for atopic dermatitis but not asthma or allergic rhinitis, when surveyed at 6 years of age. No vitamin D levels were measured in this study. These studies suggest that post-natal vitamin D levels and intake may affect the risk for development of asthma and allergies, with the larger studies suggesting that higher

vitamin D status in young children are protective of asthma and allergies as the children grow older. While most published studies report a protective effect of higher vitamin D levels or higher vitamin D intake, there are studies which suggest adverse outcomes. Clinical trials would be helpful to resolve these inconsistencies, and there are two ongoing supplementation trials in pregnancy (NCT00929621 and NCT00856947). However, there are no clinical trials that specifically address post-natal supplementation in the development of atopic disorders.

Vitamin D Deficiency and Disease Severity

Potential mechanisms for how vitamin D might decrease disease severity of asthma and allergies have been reviewed(12, 13) (Figure 2). These mechanisms include effects on immune cells, improved handling or prevention of infections, decreased inflammatory responses, and reversal of steroid resistance. Vitamin D has also been shown to have effects on airway smooth muscle mass. Gupta et al(31**) studied 86 children with a mean age of 11.6 years – 36 severe, therapy-resistant asthmatics, 26 moderate asthmatics, and 24 non-asthmatic controls. Among 19 severe, therapy-resistant asthmatics who had adequate endobronchial biopsy specimens, vitamin D levels were found to be inversely related to the airway smooth muscle mass. This finding is consistent with previous findings that vitamin D can prevent airway smooth muscle proliferation, and has implications on airway remodeling.

Several studies have examined the relationship between vitamin D deficiency and asthma exacerbations and markers of more severe disease. Brehm et al, in an analysis of data collected in 1024 participants of the Childhood Asthma Management Program (CAMP), a randomized trial of inhaled budesonide vs nedocromil vs placebo, were the first to show that vitamin D deficiency (<30 ng/ml) is associated with increased risks for severe asthma exacerbations leading to ED visits or hospitalizations(32). There appeared to be a greater effect among children who were randomized to the inhaled budesonide arm. Searing et al(33) in a cross-sectional study of 100 asthmatic children demonstrated inverse associations between vitamin D levels and serum IgE, number of skin prick tests to perennial aeroallergens, lung function, and use of inhaled or oral corticosteroids. They also showed that vitamin D enhanced glucocorticoid induction of MPK1 and IL10, critical for anti-inflammatory and immunosuppressive effects, in experiments with PBMCs. Other studies have also found lower vitamin D levels to be associated with poor asthma control(34), lower lung function and the presence of exercise-induced bronchoconstriction(35) in asthmatic children, and the severity of atopic dermatitis(36).

Two small trials have addressed the impact of vitamin D supplementation on allergic diseases. A study of 11 children with winter-related atopic dermatitis were enrolled in a pilot study of vitamin D supplementation(37). The children were randomized to 1000 IU per day of ergocalciferol or placebo for 1 month. There was a trend for improvement of atopic dermatitis scores, but due to the small number and short duration of the trial, the results did not achieve statistical significance. A study of 48 children with newly-diagnosed asthma on inhaled corticosteroids were randomized to either inhaled budesonide + 500 IU of cholecalciferol per day or inhaled budesonide + placebo for 6 months(38*). The authors found a significant reduction in the number of children who experienced an exacerbation of asthma in those assigned to the vitamin D arm, despite the fact that there were no overall differences in ATAQ scores and no significant differences in achieved 25OHD levels between groups after 6 months. There was also no definition of what constituted an asthma attack. Larger trials of sufficient duration are needed to determine whether vitamin D supplementation can affect markers of disease severity.

Vitamin D binding protein (DBP, also known as group-specific component (Gc)) is the major transport protein for vitamin D metabolites (including 25OHD), although other

proteins, such as albumin, also participate greatly in transport. Vitamin D binding protein has not previously been implicated in asthma and allergies, although it is known that DBP has immune regulating functions, related to macrophage activation and neutrophil chemotaxis(39). Recently, Lee and colleagues(40**) showed that DBP concentrations in bronchoalveolar fluid was significantly elevated in 67 asthmatic subjects compared with 22 controls. Furthermore, in a murine model, they showed that DBP mRNA and protein levels were elevated in ovalbumin-sensitized/challenged mice than in sham-treated mice, and that treatment with an anti-DBP antibody dose-dependently reduced the airway hyperreactivity, airway inflammation, and levels of eotaxin, IL-4, -5, and -13, and interferon-γ. While the implications of these results with regard to vitamin D deficiency are unclear at the moment, it is known that polymorphisms in the gene for DBP (*Gc*) are determinants of vitamin D status(41*, 42). Finally, it has been shown that DBP can regulate the bioavailability of 25OHD to cells(43**). Further studies are needed to fully understand the relationship between circulating vitamin D and DBP, and/or polymorphisms of *Gc* on asthma and allergies.

Conclusions and Future Directions

In the two years since the last review of this topic in this journal(12), the number of studies that has investigated the relationship between vitamin D and asthma and allergies has increased tremendously. An increasing number of studies have measured circulating 25OHD as a determinant of vitamin D status. However, several issues regarding the determination of vitamin D status need to be elucidated. Firstly, the level of 25OHD that determines optimal vitamin D status for asthma and allergies, and for overall health, remains elusive. While the Institute of Medicine(IOM) (44*) has recently recommended that a 25OHD level of 50 nmol/L (20 ng/ml) should be considered sufficient, this was based mainly on studies of bone health and the IOM acknowledged that studies in other disease states are sorely lacking. There is dissenting opinion to the recommendations(45*). Furthermore, there is data that suggests that optimal circulating levels may be much higher than the current IOM recommendations(46). Future studies will need to attempt to define appropriate levels rather than just using predetermined cutoffs in the analyses. Next, most studies have only measured one vitamin D level at one point in time. It is known that vitamin D levels vary over seasons, and likely over time. In an unpublished analysis in CAMP, where we measured 25OHD levels 4 years apart, the correlation between measurements is only r2=0.3, even when restricted to those whose blood draws were in the same season of the year. Thus, it is likely that levels at birth stay stable over time as the child grows. Future studies will need to measure 25OHD at multiple time points in relation to the outcome of interest.

Small trials of short duration have been conducted for asthma exacerbation and eczema. Larger trials, using adequate dosing, and of sufficient duration are needed to determine whether vitamin D supplementation decreases the risk for these exacerbations and more severe disease. Finally, results of trials of primary prevention of asthma and allergies are eagerly awaited.

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Key Bullet Points

- Vitamin D may affect asthma and allergy risk via multiple mechanisms, including lung function development and growth, optimal immune system function, enhanced response to respiratory infections, and modulation of inflammation.
- More studies have shown a beneficial effect of vitamin D on asthma and allergies than do not, although definitive clinical trials are lacking.
- The optimal dose and level of vitamin D for decreasing the burden of asthma and allergies remains unknown.

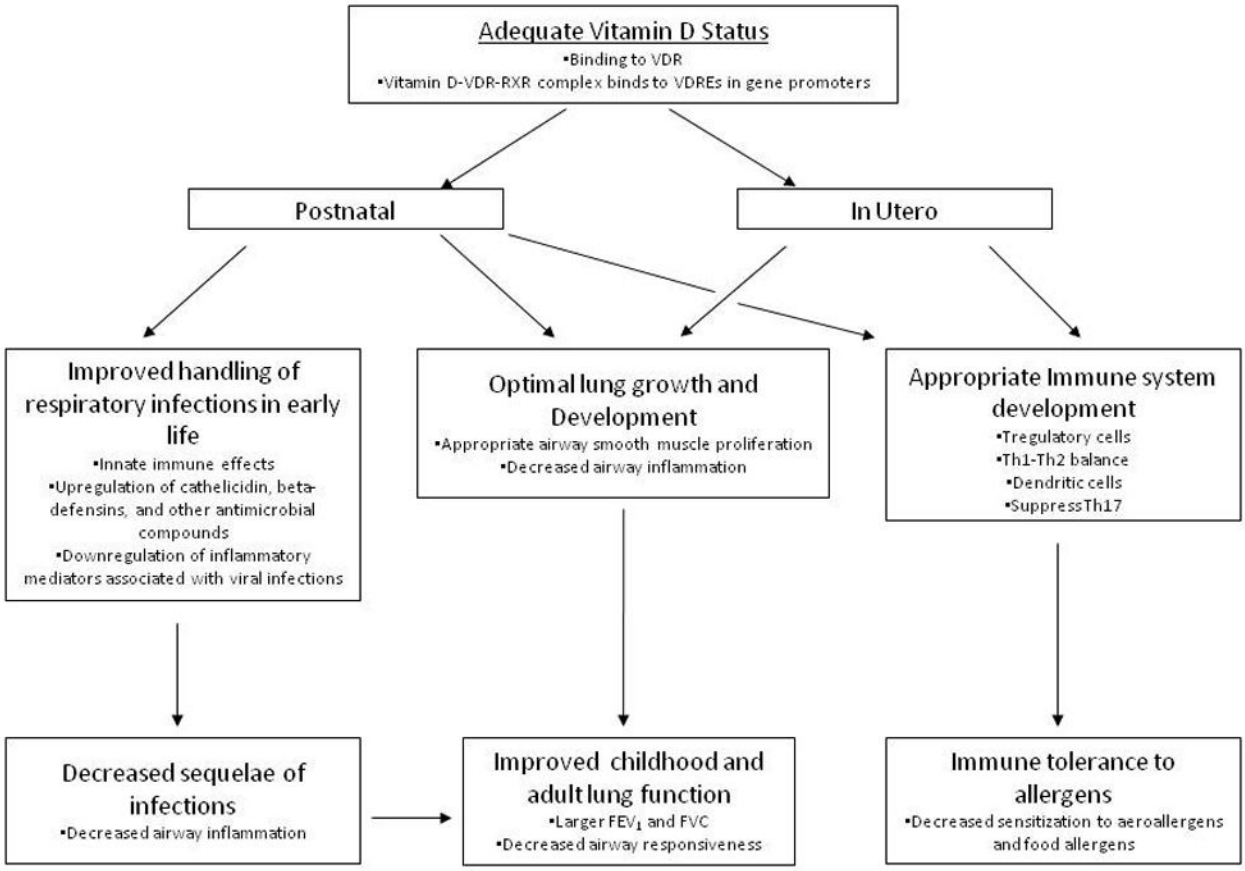

Figure 1.

Mechanisms of vitamin D in asthma and allergy development. Vitamin D has both in utero and postnatal effects that may affect the development of asthma and allergies. In the in utero period, vitamin D has been shown to play a role in lung growth and maturation. It is likely that this effect is also operating in the postnatal period. Vitamin D has effects on the developing immune system, specifically the development of Tregulatory cells and dendritic cells. The net effect of this is believed to be a balance between Th1 and Th2 responses, suppression of Th17 responses, and ultimately a decrease in sensitization. Vitamin D is also know to be critical to innate immune responses, specifically in this case, to respiratory viral infections. It has been shown that vitamin D dampens the inflammation that occurs after respiratory viral infections such as respiratory syncitial virus infections. This could lead to decreased adverse sequelae of these infections and lead to improved lung function and decreased airway responsiveness.

Modified extensively from previous work: *CML – Respiratory Medicine* 2010;24(1):1–9.

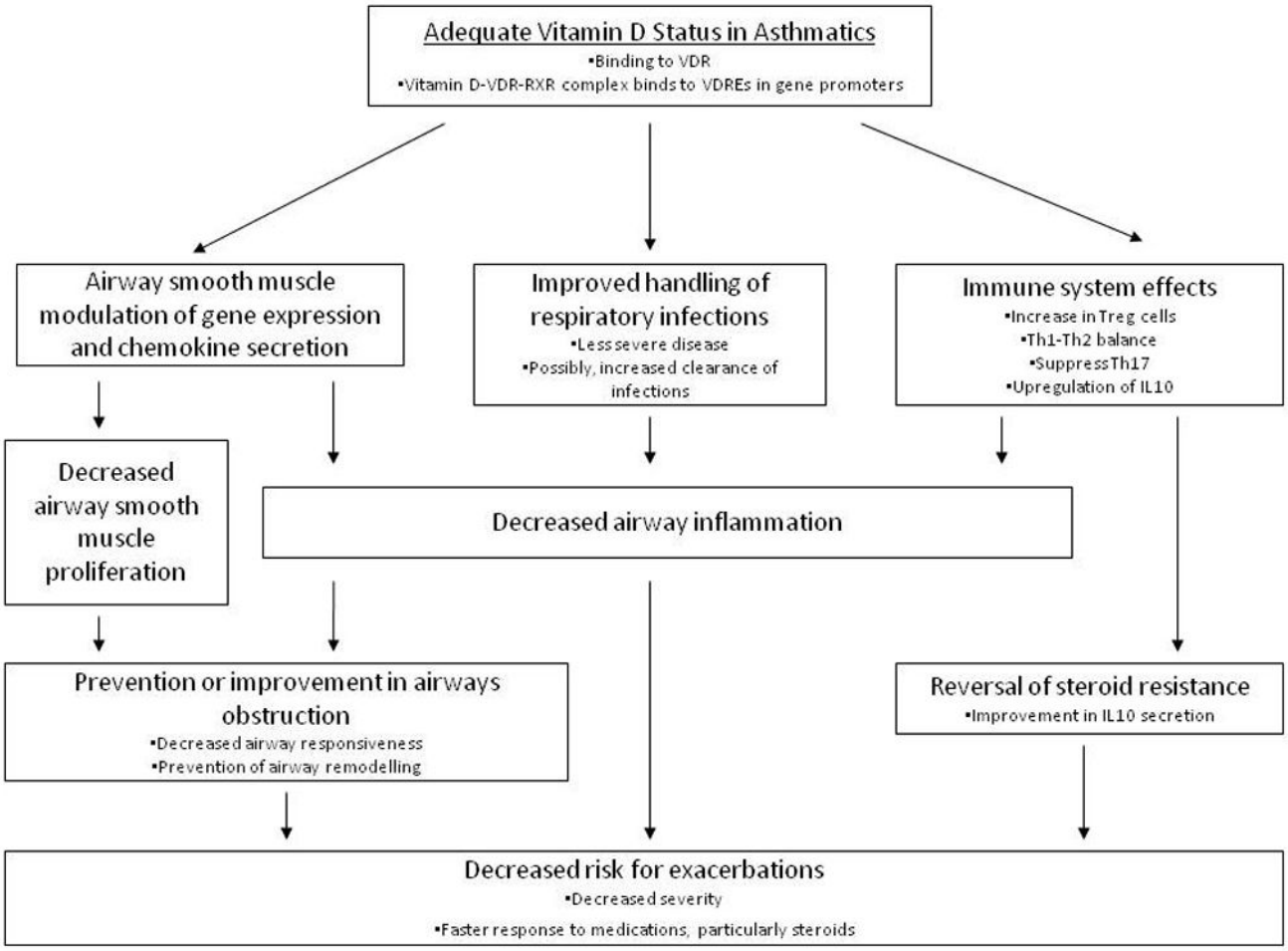

Figure 2.

Mechanisms of vitamin D in decreasing the risk for asthma exacerbations. Many of the mechanisms that are mediated by vitamin D to prevent asthma are likely operating to prevent disease exacerbations. In addition to the effects of vitamin D in improving handling of respiratory infections, improve immune cell function, decreasing inflammation, prevention of airway smooth muscle over proliferation, vitamin D has also been shown to improve the response to steroids in asthma by reversing the steroid resistant state through upregulation of IL10 production.

Modified extensively from previous work: *CML – Respiratory Medicine* 2010;24(1):1–9.