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Childhood asthma may be a consequence of vitamin D deficiency

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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

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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 D3 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 ($1,25[OH]_2D$). 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 $1\alpha,25(OH)_2D_3$ 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. Xystrakis 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, $1\alpha,25(OH)_2D_3$ 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 $1\alpha,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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 $1,25(OH)_2D_3$ 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_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 $\log_{10}$–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

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469–478. [PubMed: 15080825]

2. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980-1999. MMWR Surveill Summ 2002;51:1–13.

3. CDC. Asthma prevalence, health care use, and mortality, 2002. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2004. Edited by

4. Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007;120:1031–1035. [PubMed: 17919705]

*5. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–281. [PubMed: 17634462] This is a comprehensive review of the physiology of vitamin D and recent associations of vitamin D deficiency with a range of disorders.

6. Lamberg-Allardt C. Vitamin D in foods and as supplements. Prog Biophys Mol Biol 2006;92:33–38. [PubMed: 16618499]

7. van der Mei IA, Blizzard L, Ponsonby AL, Dwyer T. Validity and reliability of adult recall of past sun exposure in a case-control study of multiple sclerosis. Cancer Epidemiol Biomarkers Prev 2006;15:1538–1544. [PubMed: 16896046]

8. Sahota H, Barnett H, Lesosky M, Raboud JM, Vieth R, Knight JA. Association of vitamin D related information from a telephone interview with 25-hydroxyvitamin D. Cancer Epidemiol Biomarkers Prev 2008;17:232–238. [PubMed: 18199729]

9. Webb AR. Who, what, where and when-influences on cutaneous vitamin D synthesis. Prog Biophys Mol Biol 2006;92:17–25. [PubMed: 16766240]

10. Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, Holick MF, Hollis BW, Lamberg-Allardt C, McGrath JJ, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007;85:649–650. [PubMed: 17344484]

11. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28. [PubMed: 16825677]

12. Taback SP, Simons FE. Anaphylaxis and vitamin D: A role for the sunshine hormone? J Allergy Clin Immunol 2007;120:128–130. [PubMed: 17606032]

*13. Hollis BW, Wagner CL, Drezner MK, Binkley NC. 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.

14. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81:353–373. [PubMed: 16529140]

15. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Doughertly C, Gunter EW, Bowman BA. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002;76:187–192. [PubMed: 12081833]

16. US Environmental Protection Agency. Report to Congress on indoor air quality, volume II: assessment and control of indoor air pollution, Report No EPA 400-1-89-001C. Washington, DC: EPA; 1989. Edited by

17. Hollis BW, Wagner CL. Assessment of dietary vitamin D requirements during pregnancy and lactation. Am J Clin Nutr 2004;79:717–726. [PubMed: 15113709]

18. Hollis BW, Wagner CL. Vitamin D deficiency during pregnancy: an ongoing epidemic. Am J Clin Nutr 2006;84:273. [PubMed: 16895872]

19. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. Cmaj 2006;174:1287–1290. [PubMed: 16636329]

20. Sanchez PA, Idrisa A, Bobzom DN, Airede A, Hollis BW, Liston DE, Jones DD, Dasgupta A, Glew RH. Calcium and vitamin D status of pregnant teenagers in Maiduguri, Nigeria. J Natl Med Assoc 1997;89:805–811. [PubMed: 9433060]

*21. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF. Vitamin d deficiency in a healthy group of mothers and newborn infants. Clin Pediatr (Phila) 2007;46:42–44. [PubMed: 17164508] This study compared vitamin D levels in mothers and in cord blood, and found high prevalence of deficiency and high correlation between maternal levels and cord blood levels.

22. Raby BA, Lazarus R, Silverman EK, Lake S, Lange C, Wjst M, Weiss ST. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. Am J Respir Crit Care Med 2004;170:1057–1065. [PubMed: 15282200]

23. Poon AH, Laprise C, Lemire M, Montpetit A, Sinnett D, Schurr E, Hudson TJ. Association of vitamin D receptor genetic variants with susceptibility to asthma and atopy. Am J Respir Crit Care Med 2004;170:967–973. [PubMed: 15282199]

24. Vollmert C, Illig T, Altmuller J, Klugbauer S, Loesgen S, Dumitrescu L, Wjst M. Single nucleotide polymorphism screening and association analysis--exclusion of integrin beta 7 and vitamin D receptor (chromosome 12q) as candidate genes for asthma. Clin Exp Allergy 2004;34:1841–1850. [PubMed: 15663557]

25. Wjst M. Variants in the vitamin D receptor gene and asthma. BMC Genet 2005;6:2. [PubMed: 15651992]

26. Wjst M, Altmuller J, Faus-Kessler T, Braig C, Bahnweg M, Andre E. Asthma families show transmission disequilibrium of gene variants in the vitamin D metabolism and signalling pathway. Respir Res 2006;7:60. [PubMed: 16600026]

27. Wittke A, Weaver V, Mahon BD, August A, Cantorna MT. Vitamin D receptor-deficient mice fail to develop experimental allergic asthma. J Immunol 2004;173:3432–3436. [PubMed: 15322208]

28. Wittke A, Chang A, Froicu M, Harandi OF, Weaver V, August A, Paulson RF, Cantorna MT. Vitamin D receptor expression by the lung micro-environment is required for maximal induction of lung inflammation. Arch Biochem Biophys 2007;460:306–313. [PubMed: 17224129]

*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.

30. Strachan DP. Family size, infection and atopy: the first decade of the “hygiene hypothesis”. Thorax 2000;55:S2–S10. [PubMed: 10943631]

31. Ramsey CD, Celedon JC. The hygiene hypothesis and asthma. Curr Opin Pulm Med 2005;11:14–20. [PubMed: 15591883]

32. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee WM, Shult PA, Reisdorf E, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178:667–672. [PubMed: 18565953]

33. Corne JM, Marshall C, Smith S, Schreiber J, Sanderson G, Holgate ST, Johnston SL. Frequency, severity, and duration of rhinovirus infections in asthmatic and non-asthmatic individuals: a longitudinal cohort study. Lancet 2002;359:831–834. [PubMed: 11897281]
34. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin. J Immunol 2007;179:2060–2063. [PubMed: 17675463]
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]
36. Herr C, Shaykhiev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. Expert Opin Biol Ther 2007;7:1449–1461. [PubMed: 17727333]
*37. Aloia JF, Li-Ng M. Re: epidemic influenza and vitamin D. Epidemiol Infect 2007;135:1095–1096. author reply 1097-1098. [PubMed: 17352842] A brief report on a post-hoc analysis of a vitamin D clinical trial that showed that vitamin D decreased cold symptoms.
38. Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009;169:384–390. [PubMed: 19237723]
39. Dickson I. New approaches to vitamin D. Nature 1987;325:18. [PubMed: 3025744]
40. Minghetti PP, Norman AW. 1,25(OH)2-vitamin D3 receptors: gene regulation and genetic circuitry. Faseb J 1988;2:3043–3053. [PubMed: 2847948]
41. Akeno N, Saikatsu S, Kawane T, Horiuchi N. Mouse vitamin D-24-hydroxylase: molecular cloning, tissue distribution, and transcriptional regulation by 1alpha,25-dihydroxyvitamin D3. Endocrinology 1997;138:2233–2240. [PubMed: 9165006]
42. Mahon BD, Wittke A, Weaver V, Cantorna MT. The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. J Cell Biochem 2003;89:922–932. [PubMed: 12874827]
43. Heine G, Anton K, Henz BM, Worm M. 1alpha,25-dihydroxyvitamin D3 inhibits anti-CD40 plus IL-4-mediated IgE production in vitro. Eur J Immunol 2002;32:3395–3404. [PubMed: 12432570]
44. Adorini L, Penna G, Giarratana N, Roncari A, Amuchastegui S, Daniel KC, Uskokovic M. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. J Steroid Biochem Mol Biol 2004;89-90:437–441. [PubMed: 15225816]
45. Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr 2004;80:1717S–1720S. [PubMed: 15585793]
46. Matheu V, Back O, Mondoc E, Issazadeh-Navikas S. Dual effects of vitamin D-induced alteration of TH1/TH2 cytokine expression: enhancing IgE production and decreasing airway eosinophilia in murine allergic airway disease. J Allergy Clin Immunol 2003;112:585–592. [PubMed: 13679819]
47. Iho S, Kura F, Sugiyama H, Takahashi T, Hoshino T. The role of monocytes in the suppression of PHA-induced proliferation and IL 2 production of human mononuclear cells by 1,25-dihydroxyvitamin D3. Immunol Lett 1985;11:331–336. [PubMed: 3879241]
48. Reichel H, Koeffler HP, Tobler A, Norman AW. 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proc Natl Acad Sci U S A 1987;84:3385–3389. [PubMed: 3033646]
49. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 2001;167:4974–4980. [PubMed: 11673504]
50. Cantorna MT, Woodward WD, Hayes CE, DeLuca HF. 1,25-dihydroxyvitamin D3 is a positive regulator for the two anti-encephalitogenic cytokines TGF-beta 1 and IL-4. J Immunol 1998;160:5314–5319. [PubMed: 9605130]
51. Topilski I, Flaishon L, Naveh Y, Harmelin A, Levo Y, Shachar I. The anti-inflammatory effects of 1,25-dihydroxyvitamin D3 on Th2 cells in vivo are due in part to the control of integrin-mediated T lymphocyte homing. Eur J Immunol 2004;34:1068–1076. [PubMed: 15048717]
52. McGlade JP, Gorman S, Zosky GR, Larcombe AN, Sly PD, Finlay-Jones JJ, Turner DJ, Hart PH. Suppression of the asthmatic phenotype by ultraviolet B-induced, antigen-specific regulatory cells. Clin Exp Allergy 2007;37:1267–1276. [PubMed: 17845406]

53. Pichler J, Gerstmayr M, Szepfalusi Z, Urbanek R, Peterlik M, Willheim M. 1 alpha,25(OH)2D3 inhibits not only Th1 but also Th2 differentiation in human cord blood T cells. Pediatr Res 2002;52:12–18. [PubMed: 12084841]

54. Annesi-Maesano I. Perinatal events, vitamin D, and the development of allergy. Pediatr Res 2002;52:3–5. [PubMed: 12084839]

55. Gregori S, Casorati M, Amuchastegui S, Smiroldo S, Davalli AM, Adorini L. Regulatory T cells induced by 1 alpha,25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. J Immunol 2001;167:1945–1953. [PubMed: 11489974]

56. Gregori S, Giarratana N, Smiroldo S, Uskokovic M, Adorini L. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. Diabetes 2002;51:1367–1374. [PubMed: 11978632]

57. Meehan MA, Kerman RH, Lemire JM. 1,25-Dihydroxyvitamin D3 enhances the generation of nonspecific suppressor cells while inhibiting the induction of cytotoxic cells in a human MLR. Cell Immunol 1992;140:400–409. [PubMed: 1531943]

58. Schwartz RH. Natural regulatory T cells and self-tolerance. Nat Immunol 2005;6:327–330. [PubMed: 15785757]

59. Chatenoud L, Salomon B, Bluestone JA. Suppressor T cells--they're back and critical for regulation of autoimmunity! Immunol Rev 2001;182:149–163. [PubMed: 11722631]

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

61. D'Ambrosio D, Cippitelli M, Cocciolo MG, Mazzeo D, Di Lucia P, Lang R, Sinigaglia F, Panina-Bordignon P. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. J Clin Invest 1998;101:252–262. [PubMed: 9421488]

62. Xing N, Maldonado ML, Bachman LA, McKean DJ, Kumar R, Griffin MD. Distinctive dendritic cell modulation by vitamin D(3) and glucocorticoid pathways. Biochem Biophys Res Commun 2002;297:645–652. [PubMed: 12270143]

63. Yu XP, Bellido T, Manolagas SC. Down-regulation of NF-kappa B protein levels in activated human lymphocytes by 1,25-dihydroxyvitamin D3. Proc Natl Acad Sci U S A 1995;92:10990–10994. Erratum in: Proc Natl Acad Sci U S A 11996 Jan 10999;10993(10991):10524. [PubMed: 7479923]

64. Cippitelli M, Santoni A. Vitamin D3: a transcriptional modulator of the interferon-gamma gene. Eur J Immunol 1998;28:3017–3030. [PubMed: 9808170]

65. Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, Adikibi T, Pridgeon C, Dallman M, Loke TK, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. J Clin Invest 2006;116:146–155. [PubMed: 16341266]

**66. Banerjee A, Damera G, Bhandare R, Gu S, Lopez-Boado Y, Panettieri R Jr, Tliba O. Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. Br J Pharmacol 2008;155:84–92. [PubMed: 18552877] This study adds to the growing recognition that vitamin D may have therapeutic potential in asthma, particularly in steroid-resistant asthma Additionally, this study shows a direct anti-inflammatory effect of vitamin D on human airway smooth muscle cells.

**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.

68. Burri PH. Fetal and postnatal development of the lung. Annu Rev Physiol 1984;46:617–628. [PubMed: 6370120]

69. Marin L, Dufour ME, Nguyen TM, Tordet C, Garabedian M. Maturational changes induced by 1 alpha,25-dihydroxyvitamin D3 in type II cells from fetal rat lung explants. Am J Physiol 1993;265:L45–52. [PubMed: 8338181]

70. Marin L, Dufour ME, Tordet C, Nguyen M. 1,25(OH)2D3 stimulates phospholipid biosynthesis and surfactant release in fetal rat lung explants. Biol Neonate 1990;57:257–260. [PubMed: 2322608]

71. Nguyen M, Trubert CL, Rizk-Rabin M, Rehan VK, Besancon F, Cayre YE, Garabedian M. 1,25-Dihydroxyvitamin D3 and fetal lung maturation: immunogold detection of VDR expression in pneumocytes type II cells and effect on fructose 1,6 bisphosphatase. J Steroid Biochem Mol Biol 2004;89-90:93–97. [PubMed: 15225753]

72. Nguyen TM, Guillozo H, Marin L, Tordet C, Koite S, Garabedian M. Evidence for a vitamin D paracrine system regulating maturation of developing rat lung epithelium. Am J Physiol 1996;271:L392–399. [PubMed: 8843787]

73. Nguyen M, Guillozo H, Garabedian M, Balsan S. Lung as a possible additional target organ for vitamin D during fetal life in the rat. Biol Neonate 1987;52:232–240. [PubMed: 2823916]

74. Rehan VK, Torday JS, Peleg S, Gennaro L, Vouros P, Padbury J, Rao DS, Reddy GS. 1Alpha,25-dihydroxy-3-epi-vitamin D3, a natural metabolite of 1alpha,25-dihydroxy vitamin D3: production and biological activity studies in pulmonary alveolar type II cells. Mol Genet Metab 2002;76:46–56. [PubMed: 12175780]

75. Phokela SS, Peleg S, Moya FR, Alcorn JL. Regulation of human pulmonary surfactant protein gene expression by 1alpha,25-dihydroxyvitamin D3. Am J Physiol Lung Cell Mol Physiol 2005;289:L617–626. [PubMed: 15951333]

76. Gaultier C, Harf A, Balmain N, Cuisinier-Gleizes P, Mathieu H. Lung mechanics in rachitic rats. Am Rev Respir Dis 1984;130:1108–1110. [PubMed: 6508008]

77. Brun P, Dupret JM, Perret C, Thomasset M, Mathieu H. Vitamin D-dependent calcium-binding proteins (CaBPs) in human fetuses: comparative distribution of 9K CaBP mRNA and 28K CaBP during development. Pediatr Res 1987;21:362–367. [PubMed: 2437519]

78. Lunghi B, Meacci E, Stio M, Celli A, Bruni P, Nassi P, Treves C. 1,25-dihydroxyvitamin D3 inhibits proliferation of IMR-90 human fibroblasts and stimulates pyruvate kinase activity in confluent-phase cells. Mol Cell Endocrinol 1995;115:141–148. [PubMed: 8824889]

79. Stio M, Celli A, Lunghi B, Raugei G, Modesti A, Treves C. Vitamin D receptor in IMR-90 human fibroblasts and antiproliferative effect of 1,25-dihydroxyvitamin D3. Biochem Mol Biol Int 1997;43:1173–1181. [PubMed: 9442914]

80. Stio M, Lunghi B, Celli A, Nassi P, Treves C. Effect of 1,25-dihydroxyvitamin D3 on proliferation in senescent IMR-90 human fibroblasts. Mech Ageing Dev 1996;91:23–36. [PubMed: 8910257]

81. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. Chest 2005;128:3792–3798. [PubMed: 16354847]

**82. Camargo JCA, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, Kleinman K, Gillman MW. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at age 3 years. Am J Clin Nutr 2007;85:788–795. [PubMed: 17344501]

**83. Devereux G, Litonjua AA, Turner S, Craig L, McNeill G, Martindale S, Helms PJ, Seaton A, Weiss S. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr 2007;85:853–859. [PubMed: 17344509]

**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.

85. Hypponen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, Jarvelinb MR. Infant vitamin D supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Ann N Y Acad Sci 2004;1037:84–95. [PubMed: 15699498]

86. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, Godfrey KM, Cooper C. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr. 2007

**87. 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.