

Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms

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ABSTRACT

Vitamin D deficiency (VDD) has been reported in very high rates in the U.S. population. Deficiency has been implicated in various diseases such as diabetes, high blood pressure, cardiovascular disease, and many cancers. It has also been implicated in several allergic disorders and immune system dysregulation. The National Health and Nutrition examination survey (NHANES) in 2005–2006 was a cross-sectional survey performed in the noninstitutionalized population of the United States by the Center for Disease Control and Prevention and National Center for Health Statistics. It consists of an extensive interview performed at home and an examination performed at a mobile center. An allergy questionnaire was provided as interview data on self-reported allergic diseases including allergic rhinitis, allergies, and atopic dermatitis. Data were collected using the question, "Has the doctor or other health professional ever told you that you have allergies?" The laboratory parameter of vitamin D < 10 ng/mL was used to define severe VDD. The data were analyzed by logistic regression with SAS Version 9.1 (SAS Institute, Inc., Cary, NC) using the Procedure survey methods. Of 10,348 people who participated in the 2005–2006 NHANES survey, our final sample consisted of 4979 people in whom serum 25-hydroxyvitamin D levels were completed after excluding subjects <20 years of age and those with missing vitamin D values. The VDD was positively correlated with prevalence of allergies. After adjusting the model for age, gender, race, smoking, alcohol, and educational status, the odds ratio still remained significant. There was also a positive correlation with allergy subtypes such as prevalence of rashes, sneezing, and sinus infections with low vitamin D. VDD related to the immune system dysregulation has been extensively reviewed.

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This article discusses the National Health and Nutrition Examination Survey (NHANES) cross-sectional survey from 2005 to 2006 on self-reported allergic conditions, with a review of pertinent literature on vitamin D and immune mechanisms. Vitamin D₃ synthesis is highly essential for the sustenance of various physiologically important cellular and molecular processes in higher animals. Vitamin D₃-mediated biological effects occur only as a consequence of its metabolism into a family of metabolites, including the 25-hydroxyvitamin D [25(OH)D], the best measure for whole-body vitamin D status and the kidney-metabolite 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃]. Researchers consider 1,25(OH)₂D₃ to be a steroid hormone because it functions the same way as other steroid hormones—by interacting with its cognate vitamin D receptor (VDR). The role of vitamin D₃ as a vitamin or essential dietary component, in concert with the biological and clinical importance of the steroid hor-

mone 1,25(OH)₂D₃ and the VDR, has achieved increasing prominence over the past 30–40 years in the health arena because of its contributions to good health in the general public on restoration to normal levels.

VDD

Low serum 25(OH)D levels are associated with risk factors for cardiovascular disease, and they also appear to predict later development of type 2 diabetes, cancer, and an increased mortality rate.¹ Vitamin D has been reported in various disease states.^{1–4}

Hypovitaminosis D is rampant in the entire United States with a greater impact on the northeast region because of inadequate sun exposure and usage of sun protection factor cream. Vitamin D is cholecalciferol—a hormone. Deficiencies of hormones can have catastrophic consequences. Holick estimated that vitamin D deficiency (VDD) is the most common medical condition in the world and remains common in children and adults.^{3,4} Cross-sectional and prospective studies revealed the role of vitamin D insufficiency and VDD in disease states such as diabetes, hypertension, cancer, depression, osteoporosis, and heart disease. There is now overwhelming and compelling scientific and epidemiological data suggesting that the human body requires a blood level of 25(OH)D above 30 ng/mL for maximum health.³ A 25(OH)D level of 20–30 ng/mL constitutes relative insufficiency and <20 ng/mL defines the deficiency. A severe form of VDD has also

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been reported in the survey population and the previous literature implicated its role in immune system dysregulation.⁵ Moreover, recent literature redefined the biological role of this active steroid hormone and its receptor apart from its role in good bone health. There are 10 extrarenal sites for the synthesis of vitamin D and 36 cell types in various tissues that possess VDR. Because of its receptors on immune cells its exact role in immune-mediated conditions needs to be explored systematically. In addition, 1,25(OH)₂D is also a known potent immunomodulator.⁵

VDR has been found on many immune cells, such as macrophages, dendritic cells (DCs), and T and B cells, mainly after activation.⁶ The engagement of VDR on DCs was shown to shape DC phenotype and function, enhancing their tolerogenicity in adaptive immune responses.⁵ Allergen-specific immunotherapy was shown to suppress allergen-induced airway manifestations in a mouse model of allergic asthma and induced IL-10-dependent long-lasting tolerance of ovalbumin-induced asthma manifestations pointed to a role for T regulatory (T-reg) cells.⁷ Taher *et al.* were able to show that 1,25(OH)₂D₃ potentiates the efficacy of immunotherapy and that the regulatory cytokines IL-10 and transforming growth factor β play a crucial role in the effector phase of this mouse model.⁷

Our hypothesis is that low vitamin D is implicated with increased incidence of various types of allergic conditions in the NHANES self-reported adult population. This article identifies the current status of the vitamin D in subjects with allergies in the U.S. NHANES population, including its potential for contributions to good health on restoration to normal levels in these disease states. Moreover, this article provides a brief review on immune cell and VDR interactions in allergic disease.

METHODS

Survey Design

The NHANES is a continuous assessment of health and nutrition conducted by the Centers for Disease Control and Prevention and its subsidiary, the National Center for Health Statistics. Findings from this survey are used to determine the prevalence of major diseases and their risk factors. The NHANES consists of household interviews, physical and dental evaluations, and body fluid collections, such as blood and urine of a representative sample of the noninstitutionalized U.S. population, using a complex, stratified, multistage probability cluster survey design. Older individuals, children, Mexican Americans, and black Americans are purposefully overrepresented to ensure a prespecified minimum sample size. Sampling weights are used to adjust the cohort distribution so that it more closely models the U.S. population. Between 2005 and

2006, 10,348 subjects participated in the NHANES process. Those individuals <20 years old or with missing vitamin D values were excluded from data analysis. A total number of 4979 subjects that did not meet any exclusion criteria were included in final data analysis. Among them, 1210 subjects self-reported allergies.

Laboratory Methods

Serum samples were collected and analyzed in a standardized manner from fasting individuals as described in the *White Sands Clinical Laboratory's Collection Procedures and Specimen Requirements Manual*.⁸ Blood drawn from the arm was processed and stored on dry ice at -70°C . The Diasorin (formerly Incstar) 25(OH)D assay consists of a two-step procedure. The first procedure involves an extraction of 25(OH)D and other hydroxylated metabolites from serum with acetonitrile. After extraction, the treated sample is assayed by using an equilibrium radioimmunoassay (RIA) procedure. The RIA method is based on an antibody with specificity to 25(OH)D. The sample, antibody, and tracer are incubated for 90 minutes at $20-25^{\circ}\text{C}$. Phase separation is accomplished after 20-minute incubation at $20-25^{\circ}\text{C}$ with a second antibody-precipitating complex. A NSB buffer is added after this incubation and prior to centrifugation to aid in reducing non-specific binding. More detailed information about the Diasorin RIA method can be found on the NHANES website in the *Laboratory Procedures Manual*.⁹ A detailed description of the laboratory method used can be found at NHANES website in the *Laboratory Procedures Manual*.⁹

Definition of Variables

NHANES interviewers complete an extensive 2-week training course before conducting interviews. A large percentage of the interview is conducted in both English and Spanish. An allergy questionnaire provided interview data on self-reported allergic diseases including hay fever, allergies, and eczema. The data were collected using the question, "Has the doctor or other health professional ever told you that you have allergies?" and "What subtype of allergy?" The laboratory parameter of vitamin D <10 ng/mL was used to define severe VDD. This severe VDD parameter was selected to identify the existence of a statistically significant relation with allergies. Moreover, previous literature suggested the role of severity of vitamin D definition in the causation of allergies. Other covariables included were self-reported age, gender, race/ethnicity, smoking status, education status, marital status, and alcoholism. Body mass index was calculated from height and weight measurements, and placed into three categories based on the Center for Disease Control and Prevention criteria of normal (<25), overweight (25–29.9), and obese (>30).

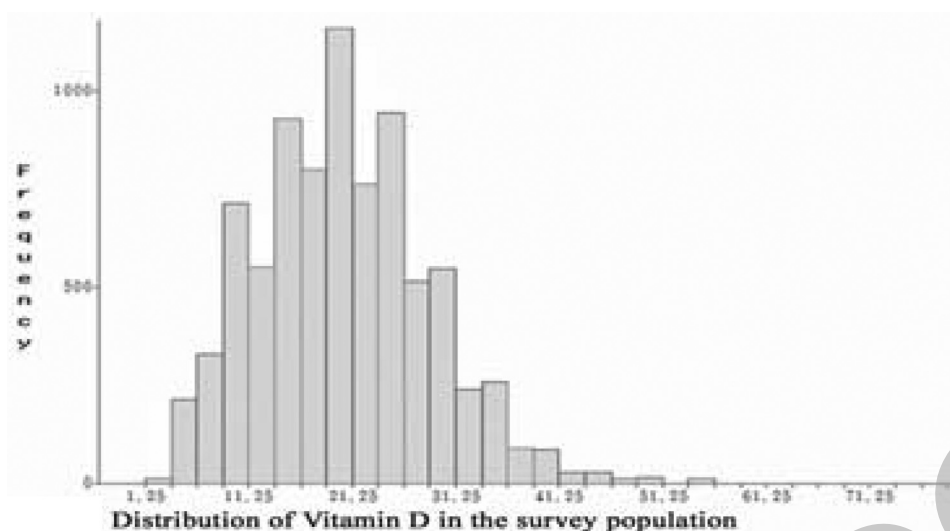


Figure 1. SAS Version 9.1 (SAS Institute, Inc., Cary, NC) generated this graph by using the function Proc survey G chart. It created the x-axis values by considering range of distribution of serum 25-hydroxyvitamin D [25(OH)D] in the population considered for analysis.

Statistical Analysis

NHANES uses a complex, stratified, multistate probability cluster sampling survey design. Because of the complexity of this survey's design, a jackknife replacement method was used to estimate the sample variance. Logistic regression models were created to look at the unadjusted association between allergies, its subtypes, and the serum levels of 25(OH)D. Adjusted regression models, using the variables age, gender, race, smoking, alcohol, and educational status, were also derived. Logistic regression analyses were performed on the study population and odds ratios (ORs) were drawn. Subanalysis was performed to establish the relationship between subtypes and vitamin D. The model was adjusted for age, race, gender, smoking status, alcohol status, and educational status. For both of the analyses we used Proc survey methods of SAS Version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

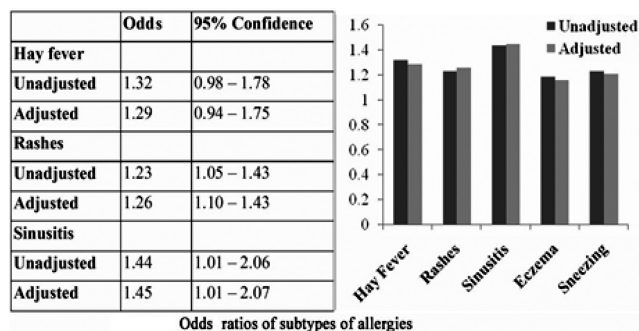
Our analysis showed the data to be normally distributed, with a right tail (Fig. 1). Of 10,348 people who participated in the 2005–2006 NHANES, our final sample consisted of 4979 people after excluding subjects <20 years of age and those with missing vitamin D values (Fig. 1). Among them, 1210 people have self-reported allergies. Black Americans and, interestingly, nonsmoker and nonalcoholic subjects have been found to be more associated with severe VDD in the allergic population (Table 1). In addition, younger subjects with allergies were found to be more deficient in vitamin D (Table 1).

VDD was positively correlated with prevalence of allergies (OR, 1.37; 95% CI, 1.14–1.69; Fig. 2). After adjusting the model for age, gender, race, smoking, alcohol, and educational status OR still remained significant (OR, 1.34; 95% CI, 1.10–1.63; Fig. 2). There was

Table 1 Demographics and baseline characteristics

	Vitamin D <10 ng/mL n (%)	Vitamin D >10 ng/mL n (%)
Age (yr)		
20–40	105 (38.47)	365 (39.74)
40–60	80 (34.59)	283 (38.62)
>60	90 (26.94)	287 (21.63)
Sex		
Male	134 (46.55)	463 (48.37)
Female	141 (53.45)	472 (51.63)
Race		
White	65 (12.59)	226 (11.74)
Black	144 (72.46)	466 (72.19)
American		
Hispanic	56 (10.38)	214 (11.81)
Other	10 (4.56)	29 (4.26)
Smoking		
Yes	53 (18.73)	227 (24.29)
No	222 (81.27)	708 (75.71)
Alcoholism		
Yes	28 (9.12)	104 (11.92)
No	247 (90.88)	831 (88.08)

also a positive correlation with prevalence of rashes (unadjusted OR, 1.23, and 95% CI, 1.05–1.43; adjusted OR, 1.26, and 95% CI, 1.10–1.43), sneezing (unadjusted OR, 1.23, and 95% CI, 1.07–1.41; adjusted OR, 1.21, and 95% CI, 1.04–1.42), and sinus infections (unadjusted OR, 1.44, and 95% CI, 1.01 to 2.06; adjusted OR, 1.45, and 95% CI, 1.01–2.07) with low vitamin D. Our study showed a positive association between VDD and prevalence of allergies. Based on the magnitude of deficiency and its association with other diseases, a careful consideration has to be given in educating the general population about vitamin D intake.



Allergies	Odds ratio (95% Confidence Intervals)
Unadjusted	1.37 (1.14 – 1.66)
Adjusted	1.34 (1.10 – 1.63)

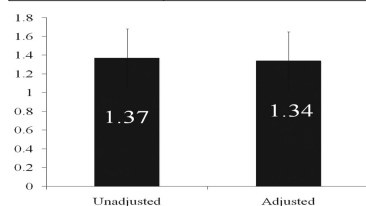


Figure 2. Note that odds ratios in a survey analysis were drawn by using the Proc survey methods in SAS Version 9.1 (SAS Institute, Inc., Cary, NC) and the function Proc survey logistic was specifically used to draw the relationship between allergies and vitamin D deficiency (unadjusted OR, 1.37, and 95% CI, 1.14–1.66; adjusted OR, 1.34, and 95% CI, 1.10–1.63) function.

DISCUSSION

The NHANES study as reviewed and a review of the existing literature is important. Vitamin D is a selective regulator of the immune system, and the outcome of $1,25(\text{OH})_2\text{D}_3$ treatment, VDD, or VDR deficiency depends on the nature of the immune response (asthma and other allergic disorders). Allergies and asthma are diseases driven by Th2 cells, and they occur when the immune system responds to different environmental antigens. Asthma is a chronic inflammatory disease of the airways. In response to airborne allergens, the immune system of an asthmatic subject generates a strong cellular response in the lung airways. Th2 cell cytokine production, inflammation, and eosinophil infiltration result in increased production of mucus, epithelial cell thickening, and, thus, airway hyperresponsiveness (vitamin D is an important immune system regulator).¹⁰

Th1 and Th2 cells are direct targets of $1,25(\text{OH})_2\text{D}_3$. Quiescent CD4^+ T cells expressed VDRs but only at low concentrations, which increased fivefold after activation.¹¹ The $1,25(\text{OH})_2\text{D}_3$ decreased the proliferation of purified Th cells and decreased the production of interferon γ , IL-2, and IL-5.¹¹ VDD has been linked to bone loss among patients with asthma and other disorders and vitamin D and/or $1,25(\text{OH})_2\text{D}_3$ supplementation is warranted for patients with asthma and other

disorders to maintain bone mineral density and to normalize circulating vitamin D concentrations.¹²

A recent article describing 25(OH)D levels in children using NHANES from 2001 to 2004 showed that 61% of children aged 1–21 years had insufficient levels of vitamin D and the prevalence of vitamin D insufficiency in children with asthma from this study population was similar to that seen in general pediatric populations living at similar northern latitudes.¹³ Xys-trakis *et al.* reported that the addition of vitamin D and dexamethasone to cultures of CD4^+ regulatory T cells from adult subjects with steroid-resistant asthma enhanced IL-10 secretion from these cells to levels comparable with those seen in cells of steroid-sensitive patients treated only with dexamethasone.¹⁴ The study also showed that vitamin D blocked dexamethasone-induced down-regulation of the glucocorticoid receptor in CD4^+ cells from healthy volunteers and when three steroid-resistant subjects were given small doses of vitamin D for 7 days, all subjects showed enhanced IL-10 expression by CD4^+ cells.¹⁴

Serum 25(OH)D levels were measured in adult urban black American subjects and white adults with chronic rhinosinusitis known to be associated with asthma and atopy which were lower, and had similar inflammatory cellular profiles consistent with a role for vitamin D in chronic sinus disease.¹⁵ They found that white female control subjects had higher serum 25(OH)D levels than black American female control subjects, and a similar nonsignificant trend between white and black American male subjects was seen, which is consistent with reported variation by ethnicity.¹⁵ Thus, deficiency of vitamin D in the winter months might partially account for the observed clinical worsening of chronic rhinosinusitis symptoms during this season, and this supports the role of vitamin D in the pathogenesis of this disease.¹⁵

Children of women living in an inner city who had VDD during pregnancy are at increased risk for wheezing illnesses.¹⁶ The pathogenesis of chronic rhinosinusitis is evidence that chronic inflammation is a histopathological finding in these patients, often similar to that seen in allergic rhinitis and asthma.¹⁶

Administration of vitamin D to subjects with steroid-resistant asthma has been reported to enhance subsequent steroid responsiveness, a finding with implications for chronic rhinosinusitis, a disease in which steroids are an important therapy. The mechanism might be related to the ability of vitamin D to promote IL-10 production by regulatory T cells, to regulate glucocorticoid receptor expression, or both. Deficiency in these pathways might partially explain decreased checks on immune responses, allowing for the abundant inflammation seen in chronic rhinosinusitis.¹⁷

Nutritional studies in pregnancy indicate that increasing maternal consumption of vitamin D decreases

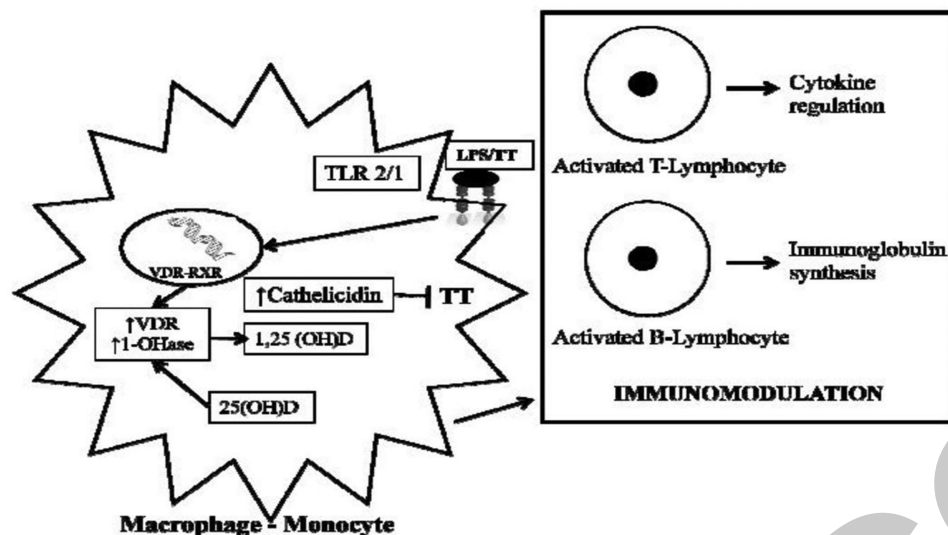


Figure 3. 1,25-Dihydroxy vitamin D [1,25(OH)₂D] produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. LPS, lipopolysaccharide; TT, tuberculosis tubercle. (Modified from Hollick MF, ref. 4.)

the risk of asthma, suggesting that *in utero* exposure might create a protective program for the developing immune system.¹⁸ Providing adequate vitamin D supplementation in pregnancy may lead to significant decreases in asthma incidence in young children.¹⁹ These and other data support the role of vitamin D in the development of asthma.²⁰

Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the VDR gene and the 25(OH)D-1 α -hydroxylase gene. Increased production of 1,25(OH)₂D₃ results in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents.² When serum levels of 25(OH)D fall below 20 ng/mL (50 nmol/L), the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D deficient, are more prone to contracting tuberculosis than are white Americans and tend to have a more aggressive form of the disease (Fig. 3).²

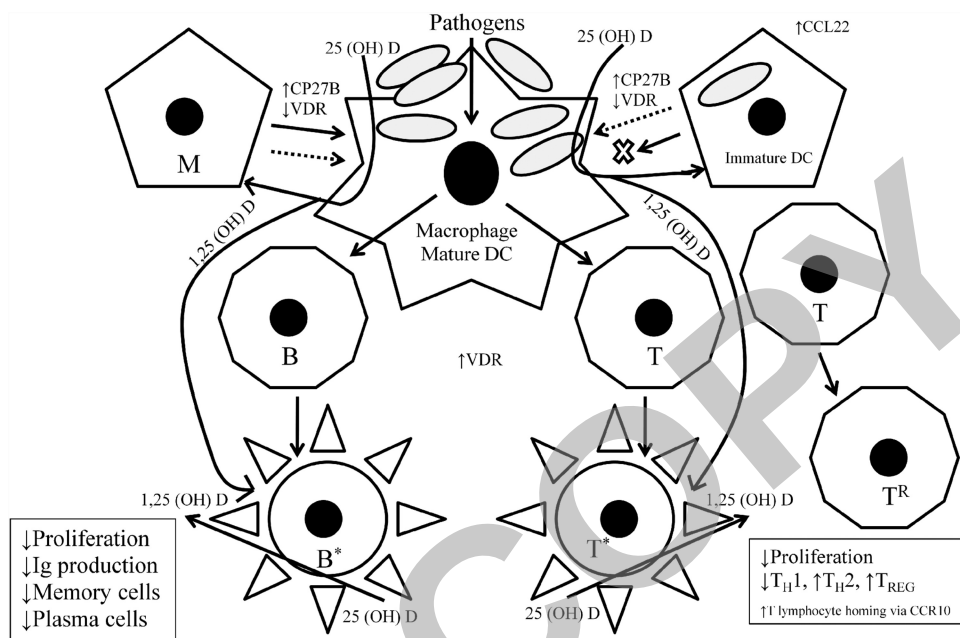
Supplementation of oral vitamin D can result in correction of defects in cathelicidins in the innate immune system of atopic subjects related to eczema.⁶ More research is needed to confirm this relationship and to further elucidate its effects on the immune system, whether it is caused by impaired white blood cell or anti-inflammatory function. Administration of oral vitamin D induces cathelicidin production in atopic individuals. The conversion of 25(OH)D to the active 1,25(OH)₂D by CYP27B1 can occur in keratinocytes and monocytes and is under the control of Toll-like receptor 2 (Fig. 3).^{21,22} Searing *et al.* reviewed the scientific evidence behind the hypothesis that vitamin D plays a role in the pathogenesis of allergic diseases, along with a focus on emerging data regarding vitamin D and atopic dermatitis.²³ It elucidated molecular interactions of vitamin D with components of the im-

mune system, and clinical data regarding VDD and atopic diseases were also discussed. Potential mechanisms were hypothesized along with the link between sunshine, vitamin D, and food allergy in children. Searing and his colleagues also reported on decrease in serum vitamin D in children with asthma that is associated with increased corticosteroid use,²⁴ which was recently reviewed²⁵ and Brehm showed that vitamin insufficiency is common in North American children with mild-to-moderate persistent asthma and is associated with higher odds of severe exacerbations.²⁶ Vassallo *et al.* suggested that concurrent with the increase in food allergy is an epidemic of VDD caused by several factors, especially decreased sunlight/UVB exposure.²⁷

There is growing appreciation of the importance of the pleiotropic hormone vitamin D in the development of tolerance, immune system defenses and epithelial barrier integrity, and a "multiple-hit" model in which VDD in a developmentally critical period increases susceptibility to colonization with abnormal intestinal microbial flora and gastrointestinal infections, contributing to abnormal intestinal barrier permeability and excess. Inappropriate exposure of the immune system to dietary allergens and early correction of VDD might promote mucosal immunity, healthy microbial ecology, and allergen tolerance and thereby blunt the food allergy epidemic in children.²⁴ Another potential role for vitamin D is suggested by the work of Schaubert who found that 1,25(OH)₂D₃ enables keratinocytes to recognize and respond to microbes through action on the Toll-like receptor 2 and leads to up-regulation of cathelicidin suggesting that VDD might be important in the predisposition of skin from patients with atopic dermatitis to superinfection by *Staphylococcus aureus*.²⁸

Széles proposed model of how exogenous or endogenously produced 1,25-vitamin D regulates gene ex-

Figure 4. Vitamin D antigen presentation along with adaptive immunity macrophages and mature DC are able to effect both T lymphocyte and B lymphocyte mediated immunity through both internalizing and processing pathogens. M, monocyte; DC, dendritic cell; B-B lymphocyte; T-T lymphocyte; B^A, activated lymphocyte; T^A, activated T lymphocyte; T^R, regulatory T cell; VDR, vitamin D receptor. (Modified from: Adams JS, and Hewison M, ref. 30.)



pression in developing DCs is that 1,25-vitamin D-regulated clusters of genes implicated in the tolerogenic phenotype (leukocyte Ig-like receptor B inhibitory receptors, human leukocyte antigen, and CD1 molecules) identified by microarray analysis.²⁹ Global gene expression analysis followed by comprehensive quantitative polymerase chain reaction validation clarified the inter-relationship between 1,25-vitamin D and differentiation-driven gene expression patterns in developing human monocyte-derived and blood myeloid DCs.²⁶ Adams showed how vitamin D is related to antigen presentation and adaptive immunity with a focus on immune cells and cytokines (Fig. 4).³⁰ Finally, an excellent review on vitamin D and the intracrinology of innate immunity was recently published by Hewison with mechanisms involved in mediating the effects of vitamin D on antigen presentation by DCs and promoting the generation of regulatory T cells.³¹ Suboptimal vitamin D status is a common feature of many populations throughout the world, with the potential to compromise monocyte/macrophage metabolism of 25(OH)D and subsequent actions of 1,25(OH)D.² The current review details these new developments with specific reference to the metabolic and signaling mechanisms associated with innate immune regulation by vitamin D and implications for human disease.³¹

A recent review article on the current literature of vitamin D and asthma discussed the possible roles of vitamin D on asthma pathogenesis and the potential consequences of VDD.³² Evidence suggests that VDD is associated with increased airway hyperresponsiveness, lower pulmonary functions, worse asthma control, and possible steroid resistance, and lung epithelial cells express high baseline levels of 1 α -hydroxylase,

allowing the conversion of inactive calcidiol to active calcitriol locally within the lung.³² Calcitriol has been shown to inhibit the synthesis and release of certain cytokines, such as regulated upon activation, normal T cell expressed and secreted, platelet-derived growth factor, and matrix metalloproteinases, from bronchial smooth muscle cells, thereby leading to decreased lung inflammation and smooth muscle cell proliferation.³² Vitamin D also increases synthesis of IL-10 by CD4⁺CD25⁺Foxp3⁺ T-reg cells and DCs, while concurrently inhibiting DC activation by down-regulating expression of costimulatory molecules CD40 and CD80/86. Vitamin D is also capable of inducing the expression of several anti-infective molecules, such as cathelicidin. Thus, vitamin D has a number of biological effects that are likely important in regulating key mechanisms in asthma. The authors hypothesized that vitamin D supplementation may lead to improved asthma control by inhibiting the influx of inflammatory cytokines in the lung and increasing the secretion of IL-10 by T-reg cells and DCs.³²

Our study showed a positive association between VDD and prevalence of allergies. Based on the magnitude of deficiency and its association with other diseases, a careful consideration must be given in educating the general population about vitamin D intake. It is of interest that nonsmokers had lower vitamin D levels as shown in Table 1 and as reported by Hutchinson.³³ Thus, this NHANES study on vitamin D with a review of the literature related to allergic disorders and immune mechanisms summarizes the importance of this study for the allergy/immunology literature.

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