# Potential mechanisms for the hypothesized link between sunshine, vitamin D, and food allergy in children

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**Epidemiologic data suggest that the incidence of food allergy (FA) is increasing among children, yet a satisfactory model of its pathogenesis remains elusive. FA is the consequence of maladaptive immune responses to common and otherwise innocuous food antigens. Concurrent with the increase in FA is an epidemic of vitamin D deficiency (VDD) caused by several factors, especially decreased sunlight/UVB exposure. 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. We propose 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 and inappropriate exposure of the immune system to dietary allergens. A compounding effect (and additional "hit") of VDD is the promotion of a pro-sensitization immune imbalance that might compromise immunologic tolerance and contribute to FA. We propose that early correction of VDD might promote mucosal immunity, healthy microbial ecology, and allergen tolerance and thereby blunt the FA epidemic in children. (J Allergy Clin Immunol 2010;126:217-22.)**

***Key words:*** *Food allergy, vitamin D, vitamin D deficiency, mucosal immunity, epithelial barrier, microbial ecology, infections, sensitization, atopy*

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The global burden of IgE-mediated food allergy (FA) is increasing.[1,2] The significant emotional, physical, and financial burdens of FA are felt in homes, schools, and health care systems.

*Abbreviations used*
FA: Food allergy
25(OH)D: 25-Hydroxyvitamin D
Treg: T regulatory cell
UVB: Ultraviolet B solar radiation
VDD: Vitamin D deficiency

Despite recent advances in our understanding of FA, many basic questions remain unanswered: Why is the incidence of FA increasing? Who will have FA? Why are young children at particular risk? How and why do some children outgrow FA? Moreover, effective interventions for FA are lacking. Primary prevention of FA by modifying the maternal diet during pregnancy appears ineffective.[3] At present, the only recommended preventive measure, with inconsistent support, is exclusive breast-feeding until 4 to 6 months of age.[3] The mainstay of secondary prevention is allergen avoidance, which can be extremely challenging. Methods to desensitize patients to food allergens are being explored, but as critical as this will be to some patients, such approaches have yet to achieve consistently safe and broadly applicable results.[4]

We propose that deficiency of the immunomodulatory hormone vitamin D might contribute to the recent increase in FA. In this article we synthesize disparate lines of epidemiologic, clinical, and basic science research in support of this hypothesis. Our objective is to stimulate discussion and additional research on this pressing problem.

## VITAMIN D DEFICIENCY

Concurrent with the recent increase in FA is an epidemic of vitamin D deficiency (VDD).[5] Vitamin D is a hormone with multiple physiologic actions,[5] the metabolites of which are stored in tissues and circulate in plasma (Table I).[6] The most abundant metabolite is a prohormone, 25-hydroxyvitamin D (25[OH]D). Levels of serum 25(OH)D are influenced most by exposure to UVB radiation in sunlight, which is necessary for synthesis of vitamin D in the skin and accounts for most vitamin D in human subjects.[7] Because of differences in UVB exposure, levels of 25(OH)D fluctuate with season (lowest in winter and highest in summer) and latitude (inversely with distance from the equator).[7,8] For example, due to absorption in the atmosphere, there is insufficient UVB intensity in most of the United States (and all of Canada and Europe) for cutaneous synthesis of 25(OH)D between the months of November and March, regardless of exposure to sunlight.[7] The precise thresholds of serum 25(OH)D that define insufficiency and deficiency are debated, but there is an emerging consensus that these thresholds should be increased,[9] particularly with recognition of vitamin D's many immunologic and noncalcemic effects.[5,10,11] Prevalence estimates vary, but in

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**TABLE I.** Characteristics of selected vitamin D metabolites

| Name | Characteristics |
|---|---|
| Vitamin D3 = cholecalciferol | Precursor of 25(OH)D; accounts for >90% of 25(OH)D in most human subjects |
| | Sources: synthesized by cutaneous epithelial cells on exposure to UVB; nutritional supplements; present in small amounts in some foods (eg, fish) |
| Vitamin D2 = ergocalciferol | Precursor of 25(OH)D |
| | Sources: nutritional supplements; present in small amounts in some foods (eg, mushrooms). |
| 25(OH)D = calcidiol | Prohormone |
| | Plasma levels exceed $1,25(OH)_2D$ by >1,000-fold |
| | Optimally calculated as the sum of 25(OH)D3 + 25(OH)D2 |
| | Useful clinically to determine sufficiency status |
| $1,25(OH)_2D$ = calcitriol | Biologically active |
| | Synthesized from 25(OH)D prohormone |
| | Production tightly controlled by regulation of metabolic enzymes |
| | Not useful clinically to determine sufficiency status |

many industrialized countries, up to 50% of the population has insufficient vitamin D, with perhaps 10% being deficient.[5,12] A recent study estimated that almost 50% of US children were vitamin D insufficient and 1 in 6 were deficient.[13]

Lifestyle changes in the latter half of the 20th century (eg, increased time indoors) have led to decreases in exposure to sunlight, which (particularly at latitudes far from the equator) have contributed to the current VDD epidemic[5] and the need for vitamin D supplementation. The re-emergence of VDD-related rickets in the 1990s led the American Academy of Pediatrics to recommend supplementation of infants with 200 IU/d in 2003, which they subsequently increased to 400 IU/d and extended to children and adolescents in 2008.[14-16] Although quantitative trend data of vitamin D status are scant, in children with chronic kidney disease (a population in which 25[OH]D levels have been routinely measured), a trend of increasing VDD has been observed.[17] Lack of widespread recognition of the diverse functions of vitamin D until recently and the challenges of vitamin D metabolite measurement[18,19] have contributed to the paucity of serum 25(OH)D trend data.

## THE VITAMIN D–FA HYPOTHESIS

In the current article we propose a model that brings together seemingly disparate research to explain how VDD might contribute to FA (Fig 1). In brief, we hypothesize that VDD, in addition to compromising immune tolerance, increases susceptibility to infections and alters microbial ecology at the mucosal site of richest antigenic exposure, the gastrointestinal tract. Gastrointestinal infections permit excessive breach of barrier and other defenses against dietary and microbial antigens in the intestinal lumen. Once in violation of defenses, these factors might synergistically promote maladaptive allergic responses to food antigens, which manifest as FA in genetically susceptible subjects.

Clinically, VDD has been linked to atopic dermatitis[20] and recurrent wheeze,[11,21,22] which are 2 components of the "atopic march" of early childhood. Another component of this pediatric disease progression is FA, which might suggest a potential role for VDD in the pathogenesis of FA as well. In 2007, Camargo et al[23] first implicated VDD as a potential risk factor for FA on the basis of (1) similar epidemiologic trends for UVB exposure and VDD (2) evidence of a striking north-south gradient in the prescription of epinephrine autoinjectors (a proxy for FA/anaphylaxis) in the United States. The epinephrine autoinjector finding was recently replicated and extended to hospitalizations for anaphylaxis in Australia.[8] Moreover, north-south gradients have been reported for both emergency department visits[24] and hospitalizations[25] for FA. Several studies have described that birth in seasons of low UVB intensity (associated with lower vitamin D levels) is more common among children reporting or given a diagnosis of FA.[26-28] Although the precise biological mechanism for these epidemiologic associations is not yet known, we hypothesize that VDD is the common biologically plausible thread and that this hormonal deficiency contributes to FA risk.

Risk factors for VDD, such as obesity and race, have been associated with food allergen sensitization. For example, the prevalence of obesity (a risk factor for VDD[29] and associated with decreased bioavailability of vitamin D metabolites[30]) has increased in children and adults over the past 20 years.[31,32] Potentially further implicating VDD in the development of FA is the observation that obesity/overweight status in children between 2 and 5 years of age is a risk factor for food allergen sensitization relative to normal-weight peers.[33] Additionally, characteristic racial variations in VDD (attributed to the effect of skin pigment on UVB penetration essential for 25[OH]D synthesis)[12,13,34] parallel FA and sensitization[2] because the prevalences of both conditions are highest among African Americans, followed by Hispanics and then non-Hispanic whites.

## VITAMIN D, THE IMMUNE SYSTEM, AND TOLERANCE

Beyond a central role in calcium and bone physiology, vitamin D metabolism, specifically conversion of 25(OH)D to the active form of vitamin D ($1,25[OH]_2D$), has effects on epithelial cell, T-cell, B-cell, and dendritic cell functions that are important to innate and adaptive immunity.[5,7,10,35-37] VDD is characterized by inadequate precursor 25(OH)D available for conversion to $1,25[OH]_2D$, which contributes to multiple pathologies (eg, osteopenia and susceptibility to infections).[5,11] The proposed contribution of VDD to the development of FA is supported by emerging data that $1,25(OH)_2D$ (1) promotes mechanisms essential for immunologic tolerance,[10,35] (2) characteristically suppresses pro-allergic immune responses,[10,36,38] and (3) maintains epithelial barrier integrity.[39] Among the vitamin D–stimulated processes that contribute to tolerance are induction of tolerogenic dendritic cells,[37] development of $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells,[10] activation of T-cell and antigen receptor signaling,[40] and elaboration of tolerizing and anti-inflammatory cytokines, including IL-10.[10,36,38] Gene expression profiles of dendritic cells have identified many $1,25(OH)_2D$-regulated transcripts central to dendritic cell function.[37] The observation that $1,25(OH)_2D$-treated human dendritic cells have the capacity to convert CD4 T cells into IL-10–secreting Treg cells and suppress the proliferation of T cells[41] is particularly provocative in light of

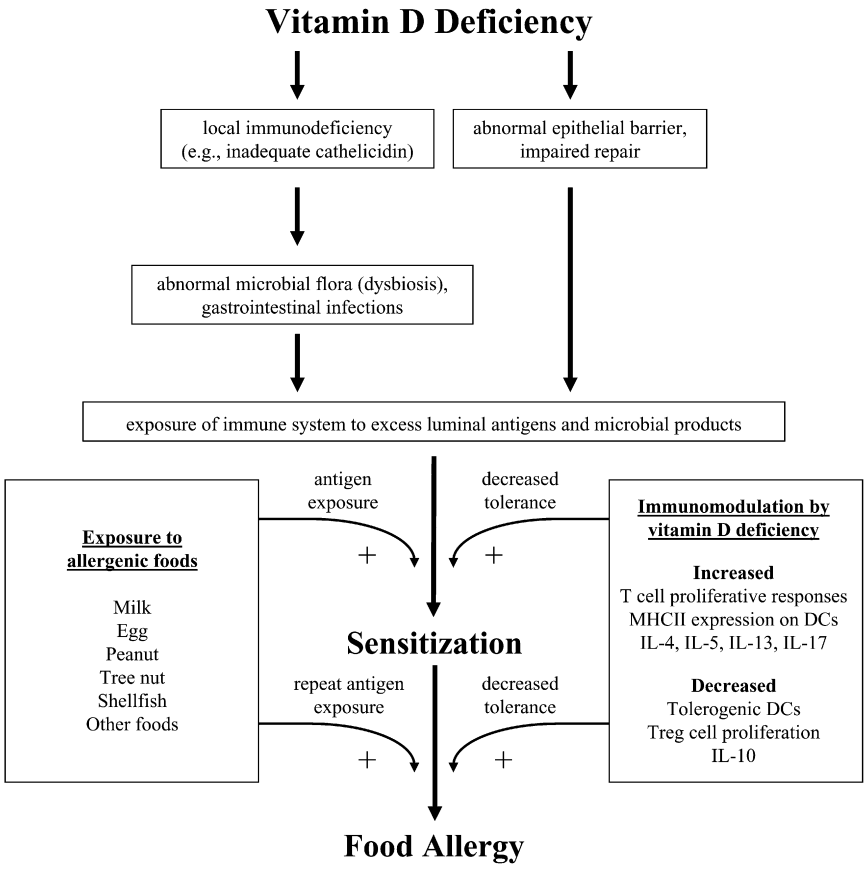


**FIG 1.** A model for the pathogenesis of childhood FA. VDD contributes to immune system defects, abnormal microbial flora, gastrointestinal infections, and compromised mucosal barrier integrity. *DC*, Dendritic cell; *MHCII*, major histocompatibility complex II molecule.

the clinical importance of $CD4^+CD25^+Foxp3^+$ Treg cells in the development of tolerance to food allergens.[42] Moreover, experiments with human B cells have demonstrated that $1,25(OH)_2D$ can directly suppress IgE production and stimulate IL-10 production.[43] Rochat et al[44] have recently linked vitamin D status during pregnancy with mechanisms of tolerance by observing that maternal intake of vitamin D was associated with expression of tolerogenic genes in cord blood.

## VITAMIN D, MICROBES, AND BARRIER FUNCTION

Vitamin D metabolites contribute to defenses at epithelial surfaces by stimulating production of antimicrobial peptides, such as defensins[45] and cathelicidin.[5,36] $1,25(OH)_2D$ influences integration of host-microbe signaling pathways by modulating expression of the microbial pattern-recognition molecules, such as NOD2,[45] CD14, and Toll-like receptor 2.[46] VDD appears to predispose to a wide variety of infections, including tuberculosis and respiratory tract viruses.[11] We speculate that VDD might similarly predispose to more frequent infections, more severe infections, or both caused by common gastrointestinal pathogens. In addition, VDD (through altered production of antimicrobial peptides) and intestinal infections might promote persistent abnormal microbial ecology or "dysbiosis."[47] Support for this proposal has recently been observed in a murine model in which VDD predisposed to colitis through dysregulated colonic antimicrobial activity and impaired homeostasis of enteric bacteria.[48]

Recent data illustrate potential mechanisms by which VDD might directly compromise barrier function in addition to increasing susceptibility to infections. Experimentally, $1,25(OH)_2D$ has been shown to have protective roles in maintenance of mucosal barrier function (regulation of tight junction proteins, including ZO-1, claudin 1, claudin 2, and E-cadherin) and response to mucosal damage.[39] Additionally, Schauber et al[46] have demonstrated an essential role of vitamin D–mediated signaling in the protective responses of wounded tissue.

Compromise of intestinal barrier function has been previously proposed to contribute to FA. For example, use of the immunosuppressant tacrolimus is associated with intestinal barrier compromise and increased risk of FA.[49] Studies have also linked other immune system abnormalities (eg, low IgA levels) with the development of childhood FA.[50] We hypothesize that VDD and infections might act synergistically to compromise intestinal barrier integrity, increase immune system exposure to food antigens, and thereby contribute to sensitization and the development of FA. It has been observed that intestinal permeability (a marker of compromised barrier integrity) and circulation of food allergens in blood increase during (and even 2 weeks after) an acute diarrheal illness in infants.[51] Mechanistically, in the setting of abnormal barrier function, microbial products might themselves promote inflammation and sensitization to food antigens as compounds derived from microbes are often used as adjuvants in experimental sensitization models.[52]

## MICROBES IN THE PATHOGENESIS OF FA

The intestinal microbiome is a community of diverse and dynamic microbe populations that participate in multiple physiologic processes, including digestion, synthesis of nutrients, and the development of the immune system[53] and tolerance.[54] The profound consequences of microbe-immune system "cross-talk" are illustrated by the observation that experimental colonization of adult mice with a single commensal bacterial species leads to induction of a subclass of T helper cells ($T_H17$).[55] An additional insight into immune system–microbe interdependence is the recent demonstration that the adaptive immune system participates in maintenance of host-microbe mutualism.[56] Support for a potential role of VDD in the alteration of population dynamics of the microbiome comes from the provocative finding that vitamin D–regulated antimicrobial peptides of the innate immune system (defensins) not only ward off pathogens but also contribute to intestinal microbiome homeostasis.[57]

Research in the field of atopic dermatitis has recently revealed exciting insights into the interplay between microbes and the innate and adaptive immune system.[58,59] For example, colonization by *Staphylococcus aureus* contributes significantly to the pathogenesis of atopic dermatitis.[58] Although we hypothesize that a VDD-related decrease in antimicrobial peptides increases the risk of infections with pathogenic organisms (eg, rotavirus or *Salmonella* species), it might also adversely affect intestinal ecology. VDD (in addition to contributing to local atopic sensitization) might foster colonization by developmentally inappropriate microbes, conditionally pathogenic microbes, or both analogous to *S aureus* in patients with atopic dermatitis. Given the multiple mechanisms by which VDD may contribute to atopic sensitization (Fig 1) and the essential role played by $1,25(OH)_2D$ in T-cell homing to the skin,[36] it is also possible that VDD contributes to cutaneous food allergen sensitization, as proposed by Lack et al,[60] although this is likely secondary because the intestine is the primary route of exposure to abundant food antigens. With the advent of molecular technologies to study the human microbiome, it is newly possible to explore the influence of vitamin D and the contributions of commensal, symbiotic, and pathogenic microbes to immunity and development of atopic diseases.

## THE IMPORTANCE OF TIMING

Laboratory investigations of mice maintained in germ-free environments have demonstrated the existence of an early window critical for development of tolerance and the importance of "natural" developmental microbial exposures.[54] These mice were unable to establish oral tolerance unless colonized with intestinal flora before the first month of life. VDD and infections at critical developmental periods might impede colonization by healthy microbial flora necessary for immune system maturation and tolerance. Adequate maturation of the immune system and establishment of a more adult intestinal microbiome might help to explain why food allergies are outgrown by some children. Although FA can develop during adulthood, this late-onset disease in a more immunologically mature host probably has a different pathogenesis than that seen in children. The likelihood of different mechanisms in early and adult FA explains our emphasis on how the proposed model applies to compromised development of tolerance (childhood onset) as opposed to loss of tolerance (adult onset).

The developing immune system might be particularly susceptible to the effects of VDD. An animal model of VDD *in utero* has shown the persistence of altered immune system development and function long after birth.[61] VDD might contribute to early-life sensitization by further compromising the immaturity of the infant immune system, which is characterized by relative IgA deficiency, low IFN-γ production, and poor humoral immunity.[62] Indeed, Nwaru et al[63] recently reported prospective data that lower levels of vitamin D in the maternal diet during pregnancy were associated with increased risk of food allergen sensitization in early childhood. Accordingly, we suspect that the relatively high prevalence of VDD among US women of child-bearing age[12] exposes their offspring to VDD and might contribute to the increasing prevalence of childhood FA.[1,2]

## EVALUATION OF THE HYPOTHESIS

Clearly, VDD is not sufficient to cause FA because conditions associated with extremely low vitamin D levels (eg, rickets and kidney disease in children) have not been linked to increased risk of any atopic diseases. Moreover, the prevalence of VDD exceeds that of FA. That said, we note that isolated VDD (without associated systemic malnutrition) is likely a phenomenon of the modern world, where the high prevalence of obesity is suggestive of nutritional excess rather than nutritional deficiency. The modern world also differs greatly from earlier times in that persons today have dissimilar diets, microbial environments, and infectious burdens.

Interdisciplinary collaborative research efforts are needed to conduct studies capable of rigorously addressing the complexity of the mechanisms we propose underlie the VDD-FA association. Research using previously disparate experimental models of the immune and protective functions of vitamin D, tolerance, intestinal inflammation, and gastrointestinal infections might serve as useful foundations for prospective clinical studies. Such studies would examine the relationships of early-life serum 25(OH)D levels, gastrointestinal infections and microbial flora, diet, food antigen–specific IgE titers, and the development and natural history of clinical FA. Ultimately, if such studies are supportive, the hypothesis will need to be tested in randomized controlled trials during pregnancy, early childhood, or both. Studies designed to identify genetic risk factors that contribute to predisposition to VDD and FA and others to explore the immunomodulatory effects of sunlight[64] beyond vitamin D metabolism might provide further insights into the complex biological processes involved.

## PREDICTIONS AND WEAKNESSES OF THE HYPOTHESIS

Children with VDD, dysbiotic microbial flora, gastrointestinal infections, and an abnormal intestinal barrier are predicted to be at increased risk of FA (Fig 1). We hypothesize that correction of VDD in early childhood might decrease the risk of FA in some subjects. However, as in atopic dermatitis, genetic variations in barrier function[65] and pro-allergic immunity are likely to be important predisposing risk factors. Unfortunately, correction of VDD (although important for other health outcomes) might not be sufficient to reverse cases of FA once pro-allergic immune pathways have been initiated.

Although there is a lack of consensus on what serum 25(OH)D threshold constitutes optimal vitamin D status,[5,9] a topic that is beyond the scope of this article, we anticipate that levels achievable by safe sun exposure, a healthy diet, and supplementation

(eg, 40 ng/mL = 100 nmol/L) will prove most salutary. We predict that correction of VDD will lower the risk of FA but caution that supraphysiologic levels of any hormone, including vitamin D, might have untoward effects, particularly during major developmental periods, such as fetal development and infancy. Supraphysiologic levels of vitamin D are achievable only by excessive supplementation and might actually increase the risk of atopic diseases, as proposed by Wjst[66] and others. We believe that these dose-specific effects and the complexity of the relationship between vitamin D, immunity, and microbes might help to explain why elucidating this hormone's role in atopic disease has proved such a challenge.

A potential weakness of the hypothesis is that given the high prevalence of VDD, the high incidence of gastrointestinal infections, and diverse mechanisms of increased intestinal permeability, one might reasonably ask why FA prevalence is less than 10% in nations with the highest burden?[3] That FA rates are as low as they are suggests that these factors are not individually sufficient for development of FA and that concurrence of these factors in early life synergize toward development of FA. This supports our view that FA is a "multi-hit" phenomenon. Accordingly, a potential reason that global populations with frequent diarrheal illness might have low/absent FA is that (in addition to other differences) they live in climates that have sufficient UVB exposure and adequate vitamin D synthesis.

Finally, our model appears discordant with the portion of the hygiene hypothesis that proposes that fewer infections increase the risk for atopic diseases. There is, however, sparse evidence to date that supports the applicability of the infection component of the hygiene hypothesis to FA.[3] Awareness of the complex dynamics of human-microbe interactions is expanding beyond the limiting categorizations of bacteria, viruses, and helminths as "pathogens," "symbionts," or "commensals" that complicate interpretation of the hygiene hypothesis. For example, distinct microbial exposures (without overt clinically evident infections) contribute to both prevention[67] and development of atopic disease.[58]

## CONCLUSIONS

The vitamin D–FA hypothesis, which began as an epidemiologic observation,[23] now integrates evidence from diverse scientific fields and provides a biologically plausible explanation for the relatively recent increase in FA. Our model is unlikely to explain the development of FA in all cases, but it can serve as a framework for potential epidemiologic and interventional studies of the interplay between VDD, subtle immune system defects, and development of FA. There are a growing number of medical reasons to address the VDD epidemic,[5] and we propose that FA might belong on this list. If future research supports our hypothesis, we believe that judicious correction of VDD during pregnancy and early childhood will promote tolerance, improve mucosal immunity, optimize microbial flora, decrease gastrointestinal infections, and thereby blunt the FA epidemic in children.

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