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