

Anaphylaxis and vitamin D: A role for the sunshine hormone?

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“The truth lies somewhere, if we knew but where....”

—William Cowper

More than a century ago, the dramatic biologic effects of sunshine and vitamin D supplementation on treating and preventing rickets, a debilitating childhood bone disease, were first established by using geographic information as a proxy for what was later recognized as vitamin D status. In addition to its classic categorization as a regulator of calcium and phosphorus metabolism and bone mineralization, vitamin D also has widespread immunomodulatory effects. These occur through a variety of different signaling pathways involving the vitamin D receptor, a member of the steroid hormone receptor family that is found in many different types of immune cells (Table I).¹⁻³ Vitamin D inhibits *in vitro* T-cell proliferation and production of cytokines such as IL-2, IL-12, and IFN- γ . Although its role in inhibition of the T_H1 immune response has been relatively well studied, its complex effects on the T_H2 response are not yet completely elucidated. In some models it induces the development of a sustained T_H2 response, yet decreases airway eosinophilia.³

The possibility of a role for vitamin D supplementation in the prevention or treatment of a number of immune-mediated diseases has been suggested. These include microbial diseases such as tuberculosis; cancers of the colon, breast, and prostate; cardiovascular diseases; some forms of arthritis; transplant rejection; and autoimmune diseases such as multiple sclerosis and type 1 diabetes.⁴⁻⁷ Vitamin D deficiency has been shown to impair insulin

synthesis, and *in vitro* investigations, studies in the nonobese diabetic mouse model, and epidemiologic studies such as a 1966 Finnish birth cohort study suggest that dietary vitamin D supplementation in early life is associated with decreased risk of development of type 1 diabetes.^{7,8} Indeed, the first randomized, controlled pilot study of vitamin D supplementation to prevent type 1 diabetes in infants with identified high-risk HLA genotypes is now underway.⁹

At this time, the role of vitamin D in the prevention or treatment of allergic diseases is not entirely clear. In the 1966 Finnish birth cohort mentioned previously, vitamin D supplementation seemed to be associated with an increased risk of atopy and allergic rhinitis later in life.¹⁰ In other cohorts, however, higher maternal intake of vitamin D during pregnancy was associated with a decreased risk of allergic diseases¹¹ and of recurrent wheeze in early childhood.¹²

In this issue of the Journal, Camargo et al¹³ promulgate the idea that vitamin D might potentially play a causative role in anaphylaxis. They used EpiPen/EpiPen Jr (Dey, Napa, Calif) dispensings as a surrogate marker for anaphylaxis, and found a significantly higher rate of dispensings in northeastern US states compared with southern states. They suggest that this reflects a higher rate of occurrence of anaphylaxis in the higher latitudes that might be associated with decreased exposure to sunshine and consequent lower vitamin D levels. One surrogate marker for sunshine exposure, estimated average melanoma incidence, correlated inversely with EpiPen dispensings, although others (average temperature data and average precipitation data) did not. Information about sunshine exposure *per se*, sunscreen use, dietary vitamin D intake, and use of vitamin D supplements was not available. Interestingly, the relatively high EpiPen dispensing rates identified in the northeastern region (ie, 10 per 1000 persons) were similar to the rate of 9.5 per 1000 persons reported in the original study using epinephrine dispensings as a surrogate marker for anaphylaxis that was conducted in the southern latitudes of Canada.¹⁴

There are some inconsistencies in the epinephrine prescription dispensing data of Camargo et al.¹³ For example, the rate in the District of Columbia (latitude 38°53'N) was approximately 10 per 1000 persons (relatively high),

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TABLE I. Signaling pathways modulated by 1,25(OH)₂D₃ in lymphocytes and antigen-presenting cells

Signaling pathway modulated by 1,25(OH) ₂ D ₃	Cell types identified	Mechanism(s) of signaling pathway modulation	Target genes
Nuclear factor κB	T cells, dendritic cells	Inhibition of total intracellular levels of multiple nuclear factor κB proteins	p105/p50, c-Rel, Rel-B
	Dendritic cells	Indirect inhibition of nuclear factor κB heterodimer binding to promoter site	IL-12 p40, (?IL-12 p35)
Nuclear factor of activated T cells	Activated T cells	Direct DNA binding of VDR/RXR and interference with NFATp/AP-1 complex assembly	IL-2, (?GM-CSF, IL-4, TNF-α)
Phosphatidylinositol-3 kinase	Promonocytic cell lines, monocytes	Activation of PI3 activity by formation of a 1,25(OH) ₂ D ₃ -dependent VDR/PI3-K complex	CD14, CD11b
Mitogen-activated protein kinase pathways	Promonocytic cell lines	Activation of ERK1/ERK2 kinase	CD14, CD11b
	T-cell hybridoma	Indirect inhibition of c-myc-mediated transcriptional activity	Fas ligand

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NFATp, Nuclear factor of activated T cells; AP-1, activator protein 1; PI-3, phosphatidylinositol-3; VDR, vitamin D receptor; PI3-K, phosphatidylinositol-3 kinase; ERK, extracellular signal-regulated kinase.

yet the rates in Virginia (latitude 36°31'N to 39°37'N) and Maryland (latitude 37°53'N to 39°43'N) were approximately 6 per 1000 persons (relatively low). Portland, Maine (latitude 43°40'), and Portland, Oregon (latitude 45°31'), had rates of 10 and 6 per 1000 persons, respectively. Nevertheless, as the authors themselves comment, these inconsistencies are perhaps not surprising in an ecologic analysis and might reflect practice variations or other factors.

We agree with Camargo et al¹³ that their multivariate analysis might not be fully controlled for socioeconomic issues. Other investigators have shown a striking association of socioeconomic status and ethnicity with the rate of occurrence of anaphylaxis.^{15,16} For example, in a study from the United Kingdom, rates of hospital admissions for anaphylaxis were significantly lower in the north (latitude ≈ 56°) than in the south (latitude ≈ 50°), and this was attributed in part to socioeconomic variations between these regions. Moreover, in a recent study of socioeconomic, racial, and ethnic factors in Massachusetts schools, minority children with peanut, tree nut, or stinging insect allergy received significantly fewer epinephrine dispensings than their white counterparts.¹⁶

Vitamin D exists in both animal (vitamin D₃, cholecalciferol) and plant (vitamin D₂, ergocalciferol) forms. The photobiology, metabolism, and mechanisms of action of the vitamin D system are well understood, and the terminology is being standardized. Sunshine, specifically UVB solar radiation in the range of 290 to 320 nm/L, transforms cutaneous 7-dehydro-cholesterol to previtamin D₃, which then isomerizes to vitamin D₃ and enters the circulation to bind with vitamin D-binding protein. In the liver, cytochrome P450-vitamin D-25-hydroxylases such as CYP27A1 convert vitamin D₃ into 25-hydroxy-vitamin D₃, the principal circulating form. Vitamin D status is

determined by measurement of 25-hydroxy-vitamin D₃. The key regulatory enzyme, CYP27B1, located in renal tubule cells, metabolizes 25-hydroxy-vitamin D₃ to 1,25-di-hydroxyvitamin D₃ (or calcitriol), the biologically active hormone and the basis for the new class of agents known as vitamin D analogues. Parathyroid hormone is the principal regulator of renal synthesis of 1,25-di-hydroxyvitamin D₃ to maintain calcium homeostasis. Paracrine synthesis of 1,25-di-hydroxyvitamin D₃ occurs in macrophages, dendritic cells, and other cells regulated in a substrate-dependent manner independently of parathyroid hormone, primarily by immune inputs, mainly IFN-γ and Toll-like receptor agonists.¹⁷

The range of 25-hydroxy-vitamin D₃ levels associated with optimal immune system function is unknown. Prevention of rickets and osteomalacia requires levels of greater than 35 nmol/L; however, physiologic studies of parathyroid hormone secretion and bone density suggest that optimal 25-hydroxy-vitamin D₃ levels for bone health are about 75 to 100 nmol/L.¹⁸ Well-designed case-control studies of individuals with multiple sclerosis⁶ or type 1 diabetes⁷ have been interpreted to suggest that prevention of these autoimmune diseases requires even higher levels of 25-hydroxy-vitamin D₃, of the order of 100 to 150 nmol/L, which are usually found only in lifeguards and other individuals who are heavily exposed to sunshine. A new upper limit of normal of 250 nmol/L has been suggested. Recent pharmacokinetic studies have shown the inadequacy of current recommended daily intakes, such as 400 IU in a multivitamin, to increase 25-hydroxy-vitamin D₃ levels in the absence of cutaneous synthesis.¹⁹

In summary, the fascinating exploratory study from Camargo et al¹³ on anaphylaxis and vitamin D, although dependent on surrogate markers, suggests that it might be important to develop and test hypotheses about the

role of the vitamin D system in this disease. Future directions for research might include further investigations in animal models (including additional studies of genes associated with allergy pathogenesis that are regulated by vitamin D metabolites)² and case-control studies involving assessment of vitamin D status in individuals who have experienced anaphylaxis versus those who have not (although asthma might be a confounder in these studies²⁰). Randomized controlled clinical trials of vitamin D supplementation in infants at high risk of allergic disease might be of interest. Wise timing of the intervention and the duration of treatment, and wise selection of the dose and formulation administered¹¹ will be necessary. Designing these trials will present scientific and ethical challenges, but in the end, the truth about the role of vitamin D in allergic diseases will be ascertained.

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Correction

With regard to the July 2007 editorial entitled "Anaphylaxis and vitamin D: A role for the sunshine hormone?" (2007;120:128-30): In the 7th paragraph (p 129), the unit of measure given for UVB solar radiation is incorrect. The relevant portion sentence should read "...in the range of 290 to 320 nm..." Please note that this error appears only in the print version of this editorial.