Perspectives in asthma

Is vitamin D deficiency to blame for the asthma epidemic?

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In the 1960s, the prevalence of asthma and allergic diseases began to increase worldwide. Currently, the burden of the disease is more than 300 million people affected. We hypothesize that as populations grow more prosperous, more time is spent indoors, and there is less exposure to sunlight, leading to decreased cutaneous vitamin D production. Coupled with inadequate intake from foods and supplements, this then leads to vitamin D deficiency, particularly in pregnant women, resulting in more asthma and allergy in their offspring. Vitamin D has been linked to immune system and lung development *in utero*, and our epidemiologic studies show that higher vitamin D intake by pregnant mothers reduces asthma risk by as much as 40% in children 3 to 5 years old. Vitamin D deficiency has been associated with obesity, African American race (particularly in urban, inner-city settings), and recent immigrants to westernized countries, thus reflecting the epidemiologic patterns observed in the asthma epidemic. Providing adequate vitamin D supplementation in pregnancy may lead to significant decreases in asthma incidence in young children. (J Allergy Clin Immunol 2007;120:1031-5.)

Key words: *Asthma, allergy, vitamin D, prevention*

Beginning in the 1960s, the prevalence of asthma and allergic diseases has increased worldwide.[1] Currently, the burden of the disease in both the developed and the developing world is significant and increasing rapidly with more than 300 million people affected worldwide, with industrialized countries furthest away from the equator (eg, Australia, New Zealand, and the United Kingdom) having the highest prevalence.[2] Asthma is one of the leading causes of morbidity in children, with 90% of all cases diagnosed by age 6 years. It remains the most common chronic disease of childhood in the world and incurs significant healthcare costs.

Abbreviations used
25(OH)D: 25-Hydroxyvitamin D_3
VDR: Vitamin D receptor
Treg: T-regulatory

The worldwide International Study of Asthma and Allergy in Children (ISAAC) studies have been helpful in showing that asthma and allergic diseases have the highest prevalence in developed countries. Much research effort has been expended in attempting to explain this pattern of the rise in asthma, and the most cited hypothesis to explain the epidemic is the hygiene hypothesis.[3] This hypothesis arose from the original observations of the inverse association between family size and atopy risk, and posits that smaller families in developed westernized countries lead to decreased exposure to infections in early life. This decreased exposure to infections in early life is supposed to result in asthma and atopy because of improper development of the immune system caused by inadequate upregulation of T_H1 immune responses and missing immune deviation from a predominantly T_H2 to a balanced T_H1/T_H2 response.[4,5] Although this hypothesis is attractive and has experimental evidence to back it, the studies on asthma have been inconsistent,[6] and it alone cannot explain all the aspects of the patterns of the asthma epidemic, such as the link between obesity and asthma, the high prevalence in poor urban environments (where children who have asthma are also at risk for infections), and the concomitant rise in T_H1-mediated autoimmune disorders. Thus, there is something else helping to drive the epidemic, and it is likely that there is another environmental exposure (or lack thereof) that can more completely explain the epidemiologic patterns of the asthma and allergy epidemic.

We hypothesize that as populations grow more prosperous and more westernized, more time is spent indoors and there is less exposure to sunlight, leading to vitamin D deficiency, subsequently resulting in more asthma and allergy. Although sunlight has many beneficial effects through several biologic pathways, to date the weight of the evidence for the link with asthma appears to be with vitamin D. Thus, prenatal deficiency of vitamin D may affect fetal lung and immune system development, and this is likely to be exacerbated by postnatal vitamin D deficiency.

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EPIDEMIOLOGY OF VITAMIN D DEFICIENCY

Vitamin D is both a nutrient and a hormone. However, unlike usual nutrients, vitamin D does not naturally occur in foods that human beings eat, except oily fish and fish liver oil, egg yolk, and offal.[7] In addition, there can be wide variation in the vitamin D content of these natural sources (eg, farmed versus wild salmon), and cooking methods (eg, frying versus baking) can deplete the amount of vitamin D in these foods.[8] Therefore, most of the vitamin D that we ingest comes from fortified foods (in the United States, milk, some milk products such as yogurt and margarine, and breakfast cereals are fortified with vitamin D[9,10]) and from supplements. The Institute of Medicine[9] currently recommends intakes of 200 IU/d from birth through age 50 years, 400 IU/d for those age 51 to 70 years, and 600 IU/d for those older than 70 years. However, there is now widespread consensus that these recommendations are woefully inadequate for overall health.[11] Currently, most experts define vitamin D deficiency as a circulating 25-hydroxyvitamin D_3 (25[OH]D) serum level of <50 nmol/L (20 ng/mL).[12] 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[OH]D) is 75 to 100 nmol/L (30-40 ng/mL)[11,13] and recommended intakes have only a modest effect on blood concentrations of 25(OH)D.[13] 25(OH)D levels of between 50 and 75 nmol/L (20-30 ng/mL) are considered relative insufficiency. The level of 25(OH)D needed for optimal immune functioning is unknown, but levels even higher than 100 nmol/L may be necessary.[14,15]

From an evolutionary standpoint, human beings do not require vitamin D in the food supply because we have a photosynthetic mechanism in the skin. 7-Dehydrocholesterol is distributed in the skin. After exposure to sunlight, specifically to the UVB range of the spectrum, 7-dehydrocholesterol is converted to previtamin D_3, which is then transformed to vitamin D_3 by a thermally induced isomerization process. Vitamin D_3 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. Many other tissues, specifically respiratory epithelial cells and cells involved in the immune response, harbor the hydroxylase and therefore are able to convert circulating 25(OH)D to 1,25-dihydroxyvitamin D_3, and have particular relevance for local immune cell signaling. Serum 25(OH)D is the major circulating metabolite of vitamin D and reflects input from cutaneous synthesis and dietary intake. Because cutaneous synthesis of vitamin D is easily affected by behaviors such as time spent indoors, clothing,[16] and sunscreen use,[17] inadequate dietary intake of this vitamin significantly magnifies the problem of deficiency.

Vitamin D deficiency has been documented in many populations worldwide,[18,19] even in areas of the world with abundant sun exposure.[20] Because of its potential role in decreasing the risk for a multitude of chronic diseases associated with westernization,[12] vitamin D deficiency is an important public health problem. Season, latitude, time of day, skin pigmentation, aging, clothing, and sunscreen use all influence the cutaneous production of vitamin D. Even in populations residing in equatorial areas, vitamin D deficiency exists and has been ascribed to behaviors such as clothing preferences (eg, women wearing veils and other concealing clothing[21,22]) and other lifestyle factors.[18,23] Vitamin D deficiency has been linked with obesity[24]; African American race,[19] particularly in inner-city settings[25]; and recent immigrants to westernized countries.[26] Therefore, the epidemiology of vitamin D deficiency appears to reflect many patterns that have been observed with the asthma epidemic. A specific segment of the population that is at risk for vitamin D deficiency is the group of pregnant women and lactating mothers, given the demands for vitamin D of the developing fetus and neonate.[27] This has added significance because deficiency in the mother is affecting both her and her child, and maternal vitamin D status may underlie the conflicting results of studies investigating breast-feeding as a risk or protective factor for asthma and allergies.[28]

VITAMIN D AND THE IMMUNE SYSTEM

Although beyond the scope of this commentary, recent extensive reviews of the effects of vitamin D on the immune system have been published.[29-32] As stated in an editorial in this Journal,[14] the role of vitamin D in inhibiting T_H1 immune responses has been well studied, but its effects on T_H2 responses are more complex and not fully elucidated. Vitamin D receptors (VDRs)[33,34] and vitamin D metabolic enzymes[18,35] have been identified in many other tissues aside from bone and the intestine, suggesting involvement in the metabolism and function of many cell types. Specifically, VDR is expressed in cells of the immune system, such as T cells,[36] activated B cells,[37] and dendritic cells.[38] The 1-α-hydroxylase is also expressed in dendritic cells,[39] suggesting that 25(OH)D can be converted to the metabolically active form locally and thus plays a role in immune signaling. Evidence exists that vitamin D induces a shift in the balance between T_H1 and T_H2-type cytokines toward T_H2 dominance,[29,40] resulting in reduced secretion of T_H1 cytokines IL-2 and IFN-γ[40-42] and an increase in the T_H2 cytokine IL-4.[43,44] In contrast, in $CD4^+$ as well as $CD8^+$ human cord blood cells, vitamin D not only inhibits IL-12–generated IFN-γ production but also suppresses IL-4 and IL-4–induced expression of IL-13.[45,46] The seemingly contradictory effects of vitamin D on T_H1-T_H2 dominance may lie, in part, in the timing of vitamin D exposure of the cells to vitamin D (ie, prenatal versus postnatal), and also in the effects of vitamin D on T-regulatory (Treg) cells. Vitamin D has been shown to promote the induction of Treg cells.[47-49] Even in a subgroup of patients who had established T_H2 disorder (eg, steroid resistant asthma), administration of vitamin D was shown to reverse steroid resistance through induction of IL-10–secreting Treg cells.[50] The effects of vitamin D

on Treg cell development and function and subsequent effects on T_H1 and T_H2 balance and function need further study.

In addition to effects on adaptive immunity, there is also a newly recognized role of vitamin D in innate immune responses to microbial agents. It is becoming apparent that vitamin D participates in Toll-like receptor signaling in response to infections by upregulating the production of cathelicidin and other antimicrobial peptides.[51-55] This effect of vitamin D is the likely explanation for the observations that sunlight can treat tuberculosis and other infections.[55,56]

These effects of vitamin D on the immune system make it a plausible critical regulator of immune system function, whose deficiency can predispose to asthma and allergies in the presence of other environmental stimuli. Because vitamin D deficiency also increases the risk for T_H1 disorders (eg, multiple sclerosis, type 1 diabetes, inflammatory bowel disease), it serves as a unifying hypothesis to explain why the incidence of both T_H1 and T_H2-related disorders has risen over the same time span. We hypothesize that in the presence of vitamin D, Treg cells develop and function normally in suppressing inappropriate T_H1 and T_H2 responses to environmental exposure (ie, allergens, lack of infections, and so forth), leading to a more balanced immune response. On the other hand, if vitamin D is lacking, Treg cells do not develop and function normally, and in the presence of the appropriate environmental influence, T_H1 or T_H2 responses are allowed to proceed unabated, leading to disease.

IS THERE EVIDENCE TO SUGGEST A LINK BETWEEN VITAMIN D AND ASTHMA?

Ecologically, many of the patterns of vitamin D deficiency appear to parallel the patterns of the asthma epidemic. Countries furthest from the equator, including Australia and New Zealand, have some of the highest rates of asthma.[2] Although Australia and New Zealand have high levels of sun exposure, vitamin D deficiency is a significant public health issue in those countries as well,[57] signifying that human behavioral patterns (ie, sunscreen use and sun avoidance behaviors) are significant determinants of vitamin D status.

Genetic studies have provided early evidence of a potential role of vitamin D in asthma. Two North American family-based studies showed associations between VDR polymorphisms and asthma,[58,59] but other studies have not found these associations.[60,61] Other genes in the vitamin D signaling pathway may also be important.[62] Vitamin D modulates many genes related to asthma and allergy.[63] On the contrary, VDR knockout mice do not develop experimental allergic asthma,[64] and the VDR appears to be necessary for induction of some forms of lung inflammation[65]; thus, further work needs to be done in this field to elucidate genetic mechanisms.

Vitamin D has multiple effects in the developing fetus. Aside from bone development, vitamin D has been shown in animal models to be critical for fetal immune system development and brain development. With regard to asthma, studies suggest that vitamin D is an important regulator of lung growth *in utero*.[66-68] Two recent analyses involving 2112 adolescents from 12 cities in the United States and Canada[69] and 14,901 adults from the National Health and Nutrition Examination Survey study[70] found that dietary vitamin D and serum vitamin D levels, respectively, were inversely associated with lung function level, suggesting the current vitamin D status may have ongoing effects on lung function. More recently, it has been demonstrated that the expression of many genes are regulated in bronchial smooth muscle cells after vitamin D stimulation, including genes previously implicated in asthma predisposition and pathogenesis.[71] More importantly, the analyses of expression data permitted the elaboration of different biological scenarios by which vitamin D may be associated with asthma, including smooth muscle cell contraction, inflammation, and glucocorticoid and prostaglandin regulation. In this last study, more comprehensive analyses indicated a network of upregulated genes with functional importance for cellular movement, cellular growth and proliferation, and cell death, which likely plays a role in airway remodeling.

We performed analyses in 2 distinct birth cohorts and found that higher maternal vitamin D intakes during pregnancy were inversely associated with wheeze prevalence in children 3 and 5 years old,[72,73] hinting that maternal vitamin D status strongly determines the risk for early wheeze phenotypes. However, we did not have serum measures of vitamin D in both these studies. Gale et al[74] found that maternal 25(OH)D in late pregnancy was inversely associated with asthma in their 9-year-old offspring. However, that study had huge loss to follow-up (61.8%), potentially biasing their results. Hypponen et al[75] found that infant vitamin D supplementation (via cod liver oil) in the first year was inversely associated with asthma and allergic conditions at age 31 years, but there was no assessment of maternal vitamin D intake or status, and no assessment of vitamin D status in the intervening period. Therefore, by using data from the two birth cohorts with maternal vitamin D assessments, we estimate that the population attributable risk for asthma incidence caused by vitamin D deficiency in pregnancy is about 40% of all cases. Although this estimate needs to be confirmed in methodologically well done studies with measures of maternal vitamin D status, we believe that there is sufficient evidence that hints at a protective effect of higher levels of vitamin D in asthma, that maternal vitamin D status is important for the respiratory health of the developing lung and the young child, and that current vitamin D status is an important determinant of current disease expression.

TESTING OUR HYPOTHESIS

We hypothesize a protective role of vitamin D in the development of asthma and allergies. However, a

detrimental effect has been postulated by others.[63] Determining the role of vitamin D in asthma will require comprehensive multidisciplinary studies. The most definitive study to test whether vitamin D plays a role in asthma pathogenesis is a clinical trial to supplement pregnant mothers with vitamin D throughout their pregnancy and following the women and their offspring through early and late childhood. Clinical trials of infant supplementation have been proposed,[63] but on the basis of our studies, we believe that earlier supplementation (during pregnancy) will be the key. The dose of vitamin D that ensures adequate vitamin D status in the mother appears to be 2000 IU/d, but maternal vitamin D status will need to be monitored by measuring 25(OH)D levels. The major toxicity of vitamin D is kidney stones, and measuring calcium-to-creatinine ratios in these mothers will be necessary. Determining the infants' vitamin D status will also be important in the context of this clinical trial because the American Academy of Pediatrics currently recommends 200 IU/d vitamin D for all infants and children and because infants' vitamin D status will depend on maternal vitamin D status and whether the infant is breast-fed.

In addition to the clinical trial, studies to determine by which mechanisms vitamin D works to decrease asthma risk should be performed. These studies include animal models, genetic association, and gene expression studies to refine the vitamin D effect on lung function (*in utero* and postnatally), smooth muscle contraction and relaxation, airway inflammation and airway remodeling, and immune cell function (particularly Treg studies). Finally, given data to suggest that vitamin D may have an effect in steroid-resistant asthma,[50] analyses of observational data to determine the potential therapeutic effect of vitamin D in asthma are also warranted, followed by clinical trials of vitamin D supplementation if the observational studies are positive.

CONCLUSION

Our hypothesis provides a new paradigm to explain not only the asthma and allergy epidemic but also a possible program for public health prevention of a substantial portion of all autoimmune and allergic disease. This hypothesis can explain the observed patterns around the world that have been reported for asthma and allergies, such as the higher prevalence of these conditions in westernized nations, in areas further away from the equator, in inner-city minority populations and immigrants to wealthy nations, and in obese subjects. More importantly, our hypothesis is also consistent with the fact that together with the rise in prevalence of T_H2-mediated disorders, the prevalence of T_H1-mediated disorders has also risen. We believe that these epidemiologic patterns can be explained by a decrease in exposure to the sun and the limited sources of vitamin D in the diet to compensate for this decrease in sun exposure leading to vitamin D deficiency in human populations.

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