Vitamin D and Allergy

Abstract

After the modern vitamin D hypothesis firstly suggested in 1999 for the allergy pandemic, numerous conditions have been thought to be associated with vitamin D deficiency such as allergy, autoimmunity and neoplasm. Consistently, previous observational studies have linked lower vitamin D status to increased markers of atopy and allergic diseases e.g. atopic dermatitis, anaphylaxis and food allergy. Vitamin D is a "hormone" having important immunomodulatory and immunoregulatory properties. In vitamin D deficient conditions, disrupted mucosal and skin complex integrity and intercurrent infections may act synergistically with allergenic exposure to amplify sensitization risk. There has been emerging data to show that vitamin D can enhance the anti-inflammatory effects of glucocorticoids and potentially be used as adjuvant therapy in steroid-resistant severe asthma. And recent in vivo data suggest that vitamin D supplementation reduce the severity of eczema and allergic rhinitis as well as urticaria symptoms. However, there is presently inadequate evidence to support daily vitamin D supplementation in the prevention and/or treatment of allergic diseases in infants, children and adolescents.

Keywords: Vitamin D; Allergy; Eczema; Asthma; Allergic rhinitis

Mini Review

Volume 3 Issue 2 - 2016

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Received: April 07, 2016 | **Published:** April 12, 2016

Introduction

After the modern vitamin D hypothesis firstly suggested in 1999 for the allergy pandemic, numerous conditions have been thought to be associated with vitamin D deficiency such as atherosclerosis, autoimmunity and neoplasm [1]. Consistently, previous observational studies have related lower vitamin D [25(OH) D3] status to increased markers of atopy and atopic diseases e.g. increased airway hyperresponsiveness, asthma, eczema, anaphylaxis, food allergy and chronic urticaria [2-4]. Furthermore, recent research on vitamin D suggests that higher serum vitamin D levels might improve some disorder outcomes such as asthma/eczema severity and urticaria symptoms; these data are somewhat questionable and conflicting [5].

Vitamin D is a "hormone" having immunomodulatory and immunoregulatory properties. In vitamin D deficient conditions, disrupted skin/mucosal complex integrity and coincidental infections might serve synergistically with allergen exposure to amplify sensitization risk at critical periods of immune development before tolerance is developed [6].

Vitamin D Deficiency

The serum 25-hydroxyvitamin D concentration is accepted as the marker of vitamin D status. In the general population, the Institute of Medicine considers that a vitamin D level >20ng/ml is sufficient for healthy bone in most individuals. Many authors assume that an optimal vitamin D status is better described by a 25OHD concentration >30ng/ml [7]. Vitamin D deficiency is more common reported worldwide than considered to be. Various estimates up to 30-80% vitamin D deficiency have been reported in the literature [6]. NHANES (2001-4) study of 6.000 individuals of 1-21 year olds in USA demonstrated 9% vitamin D deficient (<15ng/ml) and 61% vitamin D insufficient (<30ng/ml) subjects. Vitamin D levels were found to be lower in especially older children, female, African and Mexican Americans, drank milk less than once a week, more than 4 hours/day spending in front of screens [8].

Low vitamin D levels have also been demonstrated in various allergic diseases such as in asthma, eczema, allergic rhinitis, food allergy, anaphylaxis and urticaria. Whether low vitamin D levels are primary or secondary to allergic disease is not clear [2-6]. For instance: since more severe asthmatic patients spend less time outdoors, this situation is an apparent cause of vitamin D deficiency, owing to the disease [2].

Vitamin D Supplementation

Primary sun wavelengths converting vitamin D are UV-B. When someone makes vitamin D in the skin it remains 2-3 times longer in the human body. However, there is no known evidence showing any difference in disorder outcomes between the effect of oral supplements and sun exposure. Sun exposure is an ineffective mechanism of boosting vitamin D of the human body [9]. Food sources of vitamin D might be required for boosting vitamin D status in human under some circumstances e.g. cod liver oil preparations including vitamin A and D [2]. There is emerging data to show that vitamin D can enhance the anti-inflammatory effects of glucocorticoids and potentially be used as adjuvant therapy in steroid-resistant severe asthma patients. And recent in vivo data suggest that vitamin D intake can also reduce asthma exacerbations, severity of atopic dermatitis, allergic rhinitis as well as chronic urticaria symptoms [10,11].

Vitamin D Receptor Polymorphism Vitamin D receptor (VDR) and α-1- hydroxylase have been found on and in most cell types

and tissues of the body. VDRs are activated by $1,25(OH)_2D_3$ and affect expression of over 200 genes, up regulations nearly two-thirds and down regulating one-third of those genes. Therefore, VDRs found in different alleles having different effects [12,13]. A mutated VDR in hereditary vitamin D-resistant rickets prevents induction of bronchial hyper reactivity and inflammation [14]. VDR ApaI an allele is associated with better childhood asthma control and improvement in ability for daily activities [15]. Overall, these findings make us to think vitamin D's role on asthma and allergic disease development.

Pre-, Peri-, and Post-natal Vitamin D Status and Risk for Allergy

In various studies, low maternal and cord vitamin D levels were previously reported to be associated with increased risk of atopic dermatitis in infancy and wheeze and/or asthma at 3, 5, and 9 years old [2,5,8]. Allergic diseases such as asthma often begin in early childhood and are among the most common chronic childhood disorder. The incidence has increased during the last half of 20th century in developed and underdeveloped societies. Vitamin D deficiency has also become a common health problem in these societies, possibly caused by a more sedentary indoor lifestyle and decreased intake of vitamin D containing foods. Vitamin D possesses a range of immunomodulatory properties, and it has been speculated that maternal vitamin D deficiency during pregnancy may affect fetal immune system programming and contribute to the development of asthma and allergic diseases (vitamin D hypothesis) [1-3].

Supposed Immunologic Mechanisms of Vitamin D Affecting Development of Allergy

Vitamin D metabolites, [25(OH) D_3] and [1, $25(OH)_2D_3$], and receptor agonists have immunomodulatory and immunoregulatory activities [16]. The immunologic effects of VDR agonists are shown *in vitro* studies and they are able to function thru VDRs, which are widespread in the human body:

I. Innate immunity

   a. Up-regulate Toll-like receptors (TLR)

   b. Up-regulate antimicrobial proteins, maintains epithelial and mucosal barrier integrity

   c. Reduce dendritic cell maturation and migration

   d. Induce tolerogenic dendritic cells [17].

II. Th1- / Th2- cell functions

Vitamin D is well-known to inhibit Th1 cytokine release. Vitamin D's role on Th2 response and regulatory T cells (Tregs) is less comprehensible [18,19].

   A. Suppress allergen-specific IgE synthesis in vitro and in vivo environments

   B. Stimulate Th2 cytokine secretion by peripheral blood mononuclear cells [20].

   C. Suppress Th2 responses by human cord blood mononuclear cells [21].

   D. Inhibit Th1/Th2 cytokines by naïve (cord) T cells having enhanced Treg phenotype [21].

   E. Promote Treg induction which could dampen Th2 polarization [22].

   F. Enhance tolerance in adaptive immunity by up-regulating IL-10, IL-19, and TGF-β (enhancing Treg [CD4+-CD25+-FoxP3+] cell development) [23].

   a) Reduce IL-17 and IFN-γ secretions, while induce IL-4 and IL-10 cytokines [23].

III. Lymphocytes

   a. Decrease T -cell activation as well as CD40 and CD80/86 expressions on B cells

   b. Decrease T -cell proliferation

   c. Increase IL-2 production, steroid responsiveness and immunosuppressive effects [24].

IV. Mast cells: Inhibit maturation and promote apoptosis [25].

V. Eosinophils: Decrease recruitment [26].

VI. Airway epithelium and smooth muscle

   a) Inhibits smooth muscle proliferation.

   b) Decrease RANTES (CCL5) and matrix metalloproteinase production [27].

Prenatal Birth Cohorts Investigating the Effect of Vitamin D on Allergy Development The results of investigations about maternal vitamin D level effect during pregnancy on allergy development risk are not adequate and conflicting [5]. After maternal vitamin D supplementation, rate of wheezing development was found to be low at 3-5 years of age (but no relation with asthma incident at 5 years of age) [28,29]. Between maternal vitamin D 2.800 IU/day and 400 IU/day supplementation, there was no significant difference for allergy development at 3 years of age [30]. Another study performed in UK study demonstrated that high maternal plasma [25(OH) D3] level during late pregnancy was found to be associated higher risk of eczema in children at 9 months of age [31]. Maternal vitamin D and E intakes during pregnancy were detected to be associated with asthma in children [32]). Two German birth cohort studies (GINI plus and LISA plus) did not find any associations existed between serum 25(OH)D concentrations and asthma, allergic rhinitis in a sample of 2815 children at 10-years of age. But there was a positive association with the prevalence of eczema [33]. A recent meta-analysis supposes these above mentioned results as inconclusive of randomized trials of prenatal vitamin D for asthma prevention in offspring, curbing the enthusiasm [5].

Natal Umblical Cord Vitamin D Level and Wheezing Development Low cord blood 25-OH-D3 was found as a risk factor for eczema at 1-year old [34]. Cord blood vitamin D level and multi-trigger wheezing, wheezing and risk of troublesome lung symptoms development have been reported to be reversely correlated in three different studies [35,36]. However, recent two different birth cohort studies showed that cord blood vitamin D concentrations were unrelated to atopy and wheeze [37].

Postnatal Serum Low Vitamin D Status in Allergy/ Allergic Disease Development Recent studies have linked vitamin D deficiency to asthma onset and severity in children, as well as decreased pulmonary functions [4,8]. Lower levels of serum

vitamin D [25(OH)D3] have reported to be associated with increased markers of allergy and asthma severity [17,38,39].

Conflicting research showing reverse causation with normal / high Vitamin D status

On the contrary, some evidence suggests that vitamin D use / supplementation itself might increase the risk of allergic disease [2]. As mentioned above, high prenatal vitamin D status has been mostly linked to decreased risk of atopic diseases in early childhood, but whether such relations persist until adulthood has not been explored yet. In a prospective birth cohort with 965 pregnant women enrolled in 1988-1989, maternal vitamin D concentrations were quantified in serum from gestational week 30. This cohort study did not provide support for a protective effect of a high maternal vitamin D concentration on outcomes of allergic airway disease and lung function at 20 to 25 years of age. In contrast, a high maternal vitamin D concentration might be associated with an increased risk of allergic diseases in offspring [40]. During infancy, excessive vitamin D supplementation with cod liver oil was shown to be able to increase risk of asthma, food allergy and allergic rhinitis [41,42]. Northern Finland study showed that children who received vitamin D supplements during infancy had a higher risk of developing asthma, atopy and allergic rhinitis in adulthood [41]. Similarly, Swedish study showed that higher intake of vitamin D in 1st year of life was associated an increased risk of developing atopic dermatitis by age 6 years [43].

Known problems of Vitamin D research related to allergy and allergic disease

In vitamin D literature; there have been very few randomized controlled trials of allergy-related research reported nowadays. Most studies performed in this area are retrospective and do not reflect actual data for the accurate vitamin D intake/ supplementation. Many studies did not differ between vitamin D insufficiency and deficiency in their study subjects of research. Majority of studies seeking vitamin D's effect on allergic illnesses/ patients demonstrate relations/associations but not causality (cause-effect). These associations demonstrated in studies between vitamin D levels and allergy-related outcomes are shown to vary by race and other genetic as well as environmental factors [44].

Conclusion

There is presently inadequate evidence to support daily vitamin D supplementation in the prevention and/or treatment of allergic diseases in infants, children and adolescents [45]. Moreover, there are still unanswered questions such as what dose of supplemental vitamin D is optimal for prevention or control of allergy? How should these doses vary with age? Does the individual's vitamin D status have any effect on the intestinal microbiota modifying the immune system?

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