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Symposium 3: Vitamin D and immune function: from pregnancy to adolescence

Fat-soluble vitamins and atopic disease: what is the evidence?

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The prevalence of asthma and other atopic disorders continues to increase worldwide. Examination of the epidemiologic patterns has revealed that this rise has occurred primarily in western, industrialised countries and countries transitioning to this lifestyle. While many changes have occurred in human populations over the years, it has been hypothesised that some of the relevant changes that have led to the rise in asthma and atopic disorders have been the changes from a traditional diet to a more western diet consisting of decreased intake of fruits and vegetables (sources of antioxidant vitamins and carotenoids) leading to decreased intakes of vitamins E and A, and a decrease in sun exposure (e.g. greater time spent indoors and heavy use of sunscreen) leading to decreased circulating levels of vitamin D. This review will examine the evidence for an effect of fat-soluble vitamins (vitamins A, D and K) on the development and severity of asthma and allergies. While observational studies suggest that these vitamins may play a salutary role in asthma and allergies, large, well-designed clinical trials are lacking. Of the fat-soluble vitamins, vitamin D holds great promise as an agent for primary and secondary prevention of disease. Ongoing clinical trials will help determine whether results of observational studies can be applied to the clinical setting.

Vitamin E: Vitamin A: Vitamin D: Asthma: Eczema: Allergic rhinitis

Epidemiology of asthma and allergies

Asthma and allergies are common chronic diseases in industrialised countries[1–4]. In the US, recent reports from national surveys show that the prevalence of asthma continues to rise in both children and adults, and in all racial and ethnic groups[5,6]. Recently, analyses have shown that asthma incurs substantial health care costs[7,8], with estimates approaching $56 billion. While data are not as detailed as that for asthma, other allergic disorders have also shown increases. Recent National Health and Nutrition Examination Survey data showed that close to half (42·5%) of the US population are atopic[9] and both atopic dermatitis (eczema) and allergic rhinitis also incur significant healthcare costs[10,11].

Asthma and allergies have also increased worldwide[12,13]. An examination of these trends shows that the increases have been the greatest in industrialised countries and in those countries transitioning to a more industrialised lifestyle. Among the cited reasons for this pattern is a difference in diet from a more traditional diet rich in fruits and vegetables to a more 'Western' affluent diet rich in refined grains, red meats and saturated fats[13–16]. The evidence for the effect of diet on asthma and allergies is accumulating, but is far from definitive. The purpose of this paper is to review the evidence for an effect of

Abbreviations: Th, T-helper; VDR, vitamin D receptor.

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fat-soluble vitamins on asthma and allergies. There are no studies on vitamin K and asthma and allergies; thus, this review is limited to vitamins A, D and E.

Vitamin A and atopic diseases

Vitamin A comprises a group of compounds that play important roles in vision, bone growth, reproduction, cell division, cell differentiation and immune function[17–20]. In the diet, vitamin A comes in two forms, either preformed vitamin A (retinol) or pro-vitamin A carotenoid[17]. Preformed vitamin A comes from animal sources such as liver and whole milk, and from fortified foods. Pro-vitamin A carotenoid comes from plant sources in the forms of β-carotene, α-carotene, and β-cryptoxanthine.

Potential mechanisms of vitamin A in atopic diseases

Vitamin A may affect the risk for atopic disorders in two ways. Firstly, oxidative stress plays an important role in the pathogenesis of asthma and allergies[21] and the pro-vitamin A carotenoids exhibit antioxidant properties *in vitro*[22]; however, there remains some controversy as to whether they have antioxidant properties in human subjects[23]. Nevertheless, carotenoids have been investigated in conjunction with antioxidants in many human dietary studies of asthma and lung disease. Secondly, vitamin A has multiple modulatory effects on cells of the immune system (reviewed in Mora *et al.*[24]), some of which may have relevance to asthma and allergy pathogenesis. Vitamin A has been shown to enhance proliferation[25] and prolong survival[26] of human T-cells, enhance dendritic cell maturation and antigen-presenting capacity[27,28], and promote differentiation of T-regulatory cells[29,30] while inhibiting T-helper (Th) 17 cells[31]. On the other hand, vitamin A has also been shown to promote the Th2 cell responses[32,33], which are central to asthma and allergy pathogenesis.

Observational studies of vitamin A in atopic diseases

Multiple epidemiologic studies have evaluated the relationship between vitamin A (either by blood levels of constituents or estimation of intakes from food frequency questionnaires) and atopy, wheezing and asthma. Nurmatov *et al.*[34] recently performed a review and meta-analysis of these studies and found about equal numbers of studies reporting either no association or a potentially beneficial effect. Two studies have investigated maternal intakes of carotenoids in pregnancy and neither found effects on either wheezing[35,36], asthma[36] or atopic dermatitis[35] in young children.

Clinical trials of vitamin A supplementation in atopic diseases

There are no primary trials of vitamin A supplementation to prevent or manage atopic diseases. However, there have been secondary analyses of large trials of β-carotene in conjunction with antioxidants, and no effects were seen on wheezing symptoms, dypnea, lung function or asthma exacerbations[37].

Vitamin E and atopic diseases

Vitamin E is a collection of fat-soluble compounds, found in many foods, that has distinctive antioxidant activities[38]. Naturally occurring vitamin E exists in eight chemical forms (α-, β-, γ- and δ-tocopherol and α-, β-, γ- and δ-tocotrienol), of which α-tocopherol has the greatest bioavailability and is the best characterised[39]. Foods that contain vitamin E include nuts (e.g. peanuts, hazelnuts and almonds) and seeds (e.g. sunflower seeds), green vegetables (e.g. spinach and broccoli) and vegetable oils[38].

Potential mechanisms of vitamin E in atopic diseases

Vitamin E exerts its effects on the immune system by its antioxidant and anti-inflammatory properties (reviewed in Mora et al.[24] and Pekmezci[40]). Vitamin E has been shown to inhibit NF-κB pathways[41,42] and to prevent release of reactive oxygen species[43] and pro-inflammatory cytokines, such as IL-1, IL-6 and TNF[39,44,45]. Vitamin E has been shown to inhibit the secretion and gene expression of IL-4, a central cytokine in the Th2 allergic inflammatory pathway, in human peripheral blood T-cells[46], and to prevent the suppression of NRF2 (nuclear factor (erythroid-derived-2)-like 2)[47], the master transcription factor regulating expression of phase II antioxidant and detoxifying enzymes. There is some human evidence that lower intakes of vitamin E in pregnancy heightened responses of cord blood mononuclear cells to antigen stimulation[48]. This finding needs to be confirmed in other studies and the implications for the development of asthma and atopic disease need to be clarified.

Observational studies of vitamin E in atopic diseases

As oxidative stress was recognised as contributing to the pathogenesis of asthma and allergies, the effect of dietary vitamin E and other antioxidants have been studied for many years. There have been numerous studies of vitamin E and asthma and allergy symptoms and biomarkers (reviewed in Litonjua[16] and Romieu and Trenga[49]). While there have been inconsistencies, most studies have shown lower prevalence of wheezing, cough and shortness of breath in those with higher vitamin E intakes. These studies have also shown a higher lung function in those with higher vitamin E intakes. Others have shown a decreased risk for allergic sensitisation[50]. Gao *et al.*[51] performed a meta-analysis on the cross-sectional effect of vitamin E on asthma and found five studies of good quality; there was no effect of vitamin E intake on the risk for having asthma. On the other hand, in their meta-analysis, Nurmatov *et al.*[34] found a significant protective effect of maternal vitamin E intake and wheezing in 2-year-old children.

Clinical trials of vitamin E supplementation in atopic diseases

Several clinical trials of vitamin E supplementation, either alone or in combination with other antioxidants, have been conducted in asthma. Pearson *et al.*[52] randomised seventy-two adult asthmatics to either 500 mg vitamin E or placebo for 6 weeks. They did not find any effect of

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vitamin E on symptom scores, lung function, bronchodilator use or serum IgE levels. However, two other trials suggest that the effect of vitamin E may be seen only in the proper environmental context. Sienra-Monge *et al.*[53] randomised 117 asthmatic children to either 50 mg/d vitamin E plus 250 mg/d vitamin C or placebo, for 4 months. The increase in concentration of the inflammatory cytokine, IL-6, from nasal lavages in response to ozone exposure was abrogated in the intervention group compared with the placebo group. Romieu *et al.*[54], using the same dose of daily antioxidant vitamins as Sienra-Monge in 158 asthmatic children, also showed that antioxidant supplementation eliminated the lung function decrements associated with ozone exposure. These latter studies suggest that antioxidant supplementation dampens the inflammatory response to oxidant exposure in asthmatics. Finally, vitamin E supplementation (800 mg/d, compared with placebo, was found to lower nasal symptom scores in patients with seasonal allergic rhinitis[55].

While there are no published primary clinical trials of vitamin E for asthma or allergy prevention, Greenough *et al.*[56] performed a secondary analysis on 772 2-year-old children whose mothers had participated in a trial of vitamins E and C supplementation to prevent pre-eclampsia. They did not find any difference in the rates of asthma or eczema among the children from mothers in the intervention group *v.* placebo.

Vitamin D and atopic diseases

Vitamin D is both a nutrient and a hormone[57]. Vitamin D is found in only few foods that human subjects eat[58], and most vitamin D in the human diet is obtained from fortified foods and from supplements. This is likely because human subjects have the capability of producing vitamin D. 7-Dehydrocholesterol is distributed in the skin. After exposure to sunlight, 7-dehydrocholesterol is converted to pre-vitamin D_3, which is then transformed to vitamin D_3 by a thermally induced isomerisation. Vitamin D_3 then undergoes hydroxylation in the liver to 25-hydroxyvitamin D and then in the kidney to its biologically active form 1,25-dihydroxyvitamin D_3[57]. Serum 25-hydroxyvitamin D is the major circulating metabolite of vitamin D, reflects input from cutaneous synthesis and dietary intake, and measurement of levels is the standard measure of vitamin D status[59]. The determinants of vitamin D status include exposure to the sun and time spent outdoors[60,61], diet and supplement use[61], latitude, season, age, skin colour and skin coverage (i.e. clothing and sunblock use)[62]. There is controversy surrounding what is the desirable (or sufficient) level of circulating 25-hydroxyvitamin D. The recent Institute of Medicine report recommended that a level of 20 ng/ml should be considered sufficient[63]. However, since these recommendations were primarily based on bone health, with the committee concluding that there was insufficient evidence to date to make recommendations for other conditions, these recommendations were thought by some to be too low[64].

Vitamin D deficiency has been documented in many populations worldwide[65,66]. Vitamin D deficiency has occurred despite fortification of foods in some westernised countries and despite intake of multivitamins containing vitamin D, due to the fact that intake from foods and regular multivitamins are insufficient to overcome the lack of exposure to sunlight. Deficiency has also been documented in areas of the world that are considered sun-replete, and this suggests that as countries adopt a western lifestyle, there is shift from outdoor activities to more time spent indoors. For example, it is estimated that in the US alone, Americans spend an average of 93 % of their time indoors[67].

Potential mechanisms

The idea of a link between vitamin D and asthma is not new. In 1934, Rappaport *et al.* reported on 212 patients with either hay fever or both asthma and hay fever who had undergone treatment with viosterol which contains irradiated or activated ergosterol[68] (ergosterol is a plant-derived sterol that is converted to ergocalciferol (vitamin D_2) on irradiation). The goal was to increase serum Ca levels and no direct effect of vitamin D was thought to occur. While the authors reported relief of symptoms in those patients treated with viosterol, they did not detect differences in levels of serum Ca among the patients. More recently, as the physiology of vitamin D and its pleiotropic effects have been elucidated, and with the advent of the ability to measure 25-hydroxyvitamin D levels and other vitamin D metabolites, various mechanisms for how vitamin D may play a role in the development and treatment of asthma have been uncovered.

Genetics. The vitamin D receptor (VDR) is a member of the steroid receptor superfamily. The gene maps to chromosome 12. Published associations between polymorphisms in the *VDR* gene with asthma have resulted in inconsistent results[69–73], More recently, it was shown that genetic variation in genes, other than *VDR*, involved in vitamin D metabolic and signalling pathways were preferentially transmitted to asthmatic children[74].

Genetic studies have also been performed in animal models and human tissues *in vitro*. Studies in mouse models from one research group have shown that VDR knockout mice do not develop experimental asthma[75] and that expression of VDR is necessary for induction of lung inflammation[76]. On the other hand, Bossé *et al.* recently reported that VDR is present in human bronchial smooth muscle cells[77], and vitamin D regulates the expression of many genes, including genes from pathways of smooth muscle cell contraction, inflammation, as well as glucocorticoid and prostaglandin regulation.

In addition to the vitamin D pathway genes, many genes contain vitamin D responsive elements that may either up-regulate or down-regulate the expression of these genes[78,79]. For example, a recent study using chromatin immunoprecipitation followed by massively parallel DNA sequencing identified 2776 genomic positions occupied by the VDR after calcitriol stimulation; there were 229 genes with significant changes in expression in response to vitamin D[80]. Thus, the genetics of vitamin D in asthma is likely to be highly complex and far-reaching.

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Infections. The role of infections in the inception of asthma continues to be debated. Respiratory viruses have been associated with the development of asthma[81]. However, while the attack rate of respiratory viruses in early childhood is high, only a proportion of children go on to develop asthma as a consequence of these early-life infections. We have hypothesised that vitamin D status may, in part, determine who goes on to develop asthma and allergies after early-life viral respiratory infections[82]. Vitamin D induces the production of the antimicrobial polypeptide, cathelicidin[83], which has both bacterial and anti-viral effects[84,85]. Because of the effects of vitamin D on the immune system (reviewed later), it is plausible that a vitamin D-deficient state predisposes children to develop asthma after viral infections. This hypothesis will need to be tested in clinical trials of vitamin D supplementation with a collection of appropriate specimens for adequate viral identification.

Immune system effects. VDR[86,87] and vitamin D metabolic enzymes[65,88] have been identified in cells of the immune system, such as T[89], activated B-cells[90] and dendritic cells[91]. Several reviews have summarised the effects of vitamin D on immune function[24,92–94]. Vitamin D has far-ranging effects on immune cells, including modulation of Th1 and Th2 responses, induction of T-regulatory cells, suppression of Th17 cells, and regulation of maturation of dendritic cells. Directly relevant to asthma, there is evidence that vitamin D may have a therapeutic role in steroid-resistance by enhancing responsiveness to glucocorticoids for induction of IL-10[95], and modulating human airway smooth muscle secretion of pro-inflammatory chemokines[96]. An additional role of vitamin D in allergic asthma may be to potentiate the effects of allergen immunotherapy. In a mouse model of allergic asthma, co-administration of 1α,25-dihydroxyvitamin D_3 with allergen immunotherapy inhibited airway hyper-responsiveness and potentiated the reduction of ovalbumin-specific IgE levels, airway eosinophilia and Th2 cytokines[97].

Effects on lung development and lung function. Lung development begins *in utero* and continues through the first few years of life (reviewed in Burri[98]). At the end of fetal lung development, the alveolar epithelium undergoes abrupt differentiation as part of the preparation for gas exchange after birth. Fetal pulmonary maturation includes the differentiation of type II pneumocytes, with progressive disappearance of glycogen and the start of surfactant synthesis. In rat models, vitamin D is important in lung maturation and surfactant production[99–103], and in human subjects, the effect of vitamin D on surfactant production has been confirmed[104], although the mechanisms appear to be more complex than those in the rat[105].

Apart from effects on type II pneumocytes and surfactant production, vitamin D also appears to have effects on lung growth and development, as shown in studies that have measured lung mechanics in both rats [106] and mice[107]. In human subjects, vitamin D also has been shown to play a role in the developing lung. Lunghi *et al.*[108] obtained normal human fetal (16 weeks gestation) lung fibroblasts and reported that in the presence of vitamin D, pyruvate kinase activity and lactate production of the cells increased. Other findings included a decrease in cell number and DNA synthesis in the vitamin D exposed cells compared with control cells. Subsequently, they showed that the VDR was present in these human fetal fibroblasts[109]. Several large, general population-based studies have shown a positive relationship between vitamin D levels and lung function[110–112]. These findings have also been seen in asthmatic populations[113]. Other studies have found either associations with vitamin D intake but not circulating levels[114] or no associations[115].

Airway smooth muscle effects. Airway smooth muscle function is central in asthma pathogenesis. Vitamin D has been found to modulate inflammatory chemokines secreted by these airway smooth muscles[96], and has been found to inhibit airway smooth muscle proliferation in asthmatic cells[116]. Taken together, these findings suggest that vitamin D has salutary effects on airway obstruction by diminishing inflammation and decreasing airway remodelling that can lead to chronic, fixed airway obstruction.

Observational studies

Vitamin D and asthma development. Based on the effects of vitamin D on the developing immune system and the lung, it is possible that an adequate vitamin D status in pregnant mothers might prevent the development of asthma in children. Our group has reported protective effects of higher maternal dietary vitamin D intakes in pregnancy on wheezing phenotypes in young children in two separate cohorts[117,118]. These studies showed a 62 and 67% reduction in recurrent wheeze in young children born to mothers with the highest intakes of vitamin D. A third study from Finland on 1669 mother–child pairs has also shown a protective effect of higher maternal vitamin D intake on asthma in 5-year-old children[119]. Additionally, this last study also found a protective effect of higher maternal vitamin D on allergic rhinitis. A fourth study from Japan has found similar effects[120]. These studies are limited by the fact that vitamin D intake was calculated from FFQ (thus, no direct measure of vitamin D status in the mothers) and may be confounded by diet quality. However, all studies adjusted for total energy intake and for other nutrients associated with healthy diets.

Two other studies showed an adverse effect of vitamin D on asthma and allergies. A birth cohort from Northern Finland has shown that vitamin D supplementation in the first year of life increased the risk for atopy at 31 years of age[121]. However, this study did not assess maternal prenatal vitamin D status, did not assess childhood asthma or atopy, and did not have intervening measures of vitamin D status. A second study measured circulating vitamin D levels in pregnant women and reported that higher levels in pregnant women were associated with increased risks for eczema at 9 months and asthma at 9 years[122]. However, results were reported without adjustment for potential confounders, and there was significant loss to follow-up (61·8%) in the cohort at 9 years. A third study showed a protective effect of higher cord blood vitamin D levels and wheezing, but did not find an effect on incident asthma by 5 years of age[123]. Thus, the question of whether adequate

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vitamin D status can prevent asthma remains controversial and two randomised clinical trials are under way to address the issue of primary prevention (http://www.ClinicalTrials.gov: NCT00920621 and NCT00856947).

While an adequate vitamin D status in pregnant mothers may protect against the development of asthma and allergies in the offspring, there are new data suggesting that there may be opportunities to intervene after birth. Hollams *et al.*[124] in a cohort of over 600 Australian children, showed that higher vitamin D levels at age 6 years were protective against the development of asthma, rhinoconjunctivitis and atopy at age 14 years.

Vitamin D, asthma exacerbations and severity of disease. Since vitamin D affects the risk of viral infections and these infections are a cause of asthma exacerbations, the question remains as to whether improving vitamin D status can decrease the risk of exacerbations. Our group showed that higher vitamin D levels were associated with decreased risks for severe asthma exacerbations in two asthma cohorts[125,126]. Furthermore, in asthmatics, vitamin D deficiency has also been associated with higher serum IgE[125], greater degrees of airway hyper-responsiveness[125,127], lower lung function[113,127] and decreased responsiveness to glucocorticoids[126–128].

Clinical trials

Clinical trials of vitamin D supplementation as primary prevention for asthma and allergies are ongoing. A trial of vitamin D supplementation in Japanese school children showed a decrease in influenza A infections over a period of 6 months, although there was no difference in influenza B infections[129]. In the subset of children with asthma, secondary analyses found a reduction in the number of exacerbations among the children supplemented with vitamin D compared with placebo. In a small (*n* 48), 6-month clinical trial of children with newly diagnosed asthma[130], asthma exacerbations were decreased in children supplemented with vitamin D compared with placebo, despite the fact that there were no significant differences in the overall levels of circulating vitamin D achieved in either group. Verification of these preliminary results will need to be seen in larger, well-designed clinical trials of asthmatics.

Conclusion

Multiple epidemiologic studies have suggested that fat-soluble vitamins may play a role in the pathogenesis of asthma and other allergic disorders. However, large, well-designed clinical trials are lacking. Of the fat-soluble vitamins, vitamin D holds great promise as an agent for primary and secondary prevention of disease. Ongoing clinical trials will help determine whether results of observational studies can be applied to the clinical setting.

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