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Adequate Vitamin D_3 Supplementation during Pregnancy: Decreasing the Prevalence of Asthma and Food Allergies

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Abstract

Vitamin D is a secosterol that is naturally synthesized in the skin upon contact with ultraviolet rays. This vitamin can also be acquired from dietary and nutritional supplements. The active form, vitamin D3, is primarily responsible for calcium homeostasis and bone health. However, many recent studies have associated low levels of vitamin D3 with asthma and food allergies. In this review, we discuss literature to explore the potential that vitamin D3 deficiency may be contributing toward the development of asthma and food allergies. These studies indicate that mothers who supplement with doses of vitamin D3 recommended for daily consumption (400 IU) by the United States Food and Drug Administration is not enough to deliver adequate levels to breastfed infants. Because sufficient vitamin D3 serum levels correlate with a low incidence of asthma and food allergies, high dose vitamin D3 supplementation (4000 IU) by pregnant and breastfeeding women may limit the development of asthma and food allergies in newborns.

Keywords: Vitamin D; Food Allergy; Asthma; Pregnancy; Neonatal

Introduction

Our literature review explores current evidence that vitamin D insufficiency increases the risk of food allergies and asthma as well as the potential use of vitamin D prophylactic therapy for the prevention of allergic diseases.

Physiology of food allergies

Food allergies are a hypersensitivity reaction of the adaptive immune system in response to foreign antigenic molecules referred to as allergens. During the first exposure to an allergen, dendritic cells in the gastrointestinal tract prime T-helper-2 cells to trigger production of interleukins 4, 5, and 13 by CD4+ T cells [1,2]. Allergen-specific IgE antibodies become attached to mast cells following sensitization. These armed mast cells are located throughout the skin, gut, respiratory, and cardiovascular systems [2]. Upon subsequent exposure to the allergen, biomediators, such as histamine and cytokines, are released by these mast cells resulting in anaphylactic effects on endothelium, smooth muscle, and epithelium [3].

In recent years, there has been a significant public health concern due to the rise of food allergy. According to a study released in 2013 by the Centers for Disease Control and Prevention, the incidence of food allergies among children increased 50% from 1997 and 2011[4]. Every 3 minutes, an allergic reaction to a food or a food additive sends someone to the emergency department [5]. Food allergies result in over 300,000 ambulatory-care visits a year [6]. While the exact prevalence is unknown, recent estimates suggest that 15 million people in North America are affected by food allergies. Health care costs for related childhood food allergies reaches approximately $ 25 billion annually [6,7]. Ongoing research seeks to find non-invasive and prophylactic means to reduce the incidence of food allergies [8,9].

Recently there has been a tremendous increase in the public awareness of food allergies. In 2004 congress passed the Food Allergen Labeling and Consumer Protection Act (FALCPA) [10]. This law requires that labels on foods must identify the sources of all ingredients that are or contain any protein derived from the eight most common food allergens. These include milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. This allows people who have food allergies the opportunity to read these labels and avoid ingestion of allergens.

Even with the appropriate diet, lifestyle changes, and the presence of the FALCPA labels, accidental ingestion of foods that induce allergic reactions still occurs. Ingestion of this food by someone sensitive to the accompanying allergens could bring upon the onset of various symptoms that range from mild to life threatening. These allergic reactions are associated with the presence of anaphylaxis, and symptoms can include urticaria, angioedema of the face, tongue, or lips, difficulty breathing, loss of consciousness, and even death. Accurate management of food allergies is critical due to the potential for serious adverse reactions. Injectable epinephrine is the drug of choice for initial management of anaphylaxis due to food allergies and should be carried at all times by those afflicted. Other treatment methods include antihistamines, bronchodilators, and corticosteroids. The only way to prevent a reaction in the presence of an establised food allergy is by strict avoidance of the known allergen. Sometimes this may prove difficult especially with young children. Therefore, managing food allergies requires dietary and lifestyle changes by the person with a food allergy and many times the whole family.

Asthma

Asthma is a non-communicable disease with an unknown etiology that affects more than 7 million children in the United States per year.

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Genetic predispositions and various environmental exposures, such as tobacco smoke, air pollution, or chemical exposures can render an individual susceptible to asthma [11]. In asthma, limitation of airflow is caused by a variety of physiological changes including airway bronchoconstriction, edema, hyper-responsiveness, and remodeling. The primary clinical symptom of asthma is bronchoconstriction. Exposure to a variety of stimuli can cause an acute exacerbation of an individual's asthma and lead to smooth muscle contraction that narrows the airways [12]. The narrowing of the airways produces symptoms including wheezing, chest tightness, coughing and shortness of breath. As the disease progresses, the airways become inflamed leading to structural changes that pose a threat to treatment options [11].

A Medical Expenditure Panel Survey from 2002 to 2007 revealed that asthma is a substantial health problem and represents a significant economic burden in our society. With these cases worsening over the years, calculations in 2007 showed that individuals with asthma spent $ 3,259 dollars per year out of the total asthma medical burden of $ 56 billion dollars. The largest expenditure paid for prescription drugs, followed by inpatient hospitalization stays and office-based visits [13]. Efforts to prevent asthma or limit the incidence of this disease could reduce this enormous healthcare and financial burden.

Vitamin D_3

Vitamin D is a secosterol synthesized endogenously in the skin through ultraviolet ray contact. Moreover, this vitamin can be acquired through nutritional supplements, or from foods fortified with vitamin D. The two forms of this vitamin group most important for human health are Vitamin D_3 (cholecalciferol) and D_2 (ergocalciferol). Vitamin D_2 is a commonly acquired via consumption of mushrooms and dietary supplementation whereas D_3 is synthesized through skin exposure to UVB light, supplementation, and consumption of foods such as oily fish, cheese, beef liver, and egg yolks [14,15].

Vitamin D that comes from the UVB contact with the skin or diet is naturally inert and requires two hydroxylation reactions to be rendered functional. Once reaching the intestines, vitamin D is absorbed, metabolized in the liver and modified to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is comprised of 25(OH)D_2 and 25(OH) D_3. Furthermore, 1α-hydroxylase enzyme catalyzes the conversion of 25(OH)D_3 (calcidiol) to 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$] (calcitriol) in the kidney and other specific tissues.

The primary effects of vitamin D are mediated through endocrine and autocrine properties of calcitriol through stimulation of vitamin D receptors [14,15]. Vitamin D is predominantly responsible for calcium homeostasis and bone health. This secosteroid fosters intestinal absorption of calcium. In addition, Vitamin D facilitates normal bone mineralization while inhibiting hypocalcemic tetany through serum calcium and phosphate concentration regulation [14,15]. Calcium regulation and absorption is achieved in the intestines by the use of transcellular and passive paracellular pathway mechanisms through tight junctions. Calcitriol controls calcium absorption through calcium influx, transient receptor potential vanilloid type 6 (TRPV6), calcium transmission via the intracellular structure of enterocytes, and basolateral purging of calcium by the enteric plasma membrane pumps. Within the intestinal cell, calcium transmission is facilitated by the protein calbindin-D9k. Extracellular basolateral purging of calcium is enabled via enteric plasma membrane pump PMCA1b [16]. Calcitriol [1,25$(OH)_2D_3$] also works in conjunction with parathyroid hormone (PTH) by increasing the rate at which inorganic phosphate (P_i) is excreted by the kidneys. The excretion of P_i lowers serum phosphate levels which subsequently triggers hydroxyapatite [$Ca_5(PO_4)_3OH$] to dissolve from the bone increasing serum calcium levels [16].

Only 10-15% of nutritional calcium and 60% of phosphorus can be absorbed in the absence of, Vitamin D underscoring the critical role for this vitamin in bone maintenance and various other physiological functions [16]. In addition to this classical role in bone health, vitamin D may also exhibit important immunomodulatory properties, limiting the development of asthma and food allergies [17].

Vitamin D_3 deficiency

Hypovitaminosis D, commonly known as vitamin D_3 deficiency, can result in the weakening of bones due to disruption of calcium homeostasis [18]. The normal amount of vitamin D_3 is a blood serum level of at least 20 ng/ml to 60 ng/ml. A level of 12 ng/ml or less is an indication of scarcity [14]. A drop in vitamin D_3 serum levels can lead to poor development of the musculoskeletal system such as rickets in children and osteomalacia in adults [18]. The major causes of vitamin D_3 deficiency are decreased sunlight due to certain demographic locations, increased amount of melanin (dark skin pigmentations), and poor dietary intake [18]. Diminishing UVB radiation into the skin by lack of sun or applying sunscreen consequently inhibits the synthesis of vitamin D_3. In addition, an increased amount of melanin and residing in geographic areas with high latitudes limits the synthesis of vitamin D_3 as well [14]. A decrease in vitamin D_3 does not only affect the musculoskeletal system, but can also be a prequel to health complications such as cancer, autoimmune diseases, neurological dysfunctions, cardiovascular diseases, and an increased susceptibility to infections [19].

Approximately 20 to 80 percent of people worldwide are deficient in vitamin D_3. The insufficiency affects a vast range of people consisting of children, elderly, pregnant women, and most significantly breastfed infants [20]. It is vital for pregnant women to ensure they are receiving vitamin D_3 adequately for their wellbeing as well as the healthy development of their baby. Human breast milk contains 40 to 50 IU/l of vitamin D_3 [21]. Infants who receive milk from lactating mothers but are not receiving enough supplemental vitamin D_3 or exposure to sunlight are still at risk in becoming deficient [18]. Therefore, many physicians recommend supplementation of vitamin D_3 for the development of a strong immune system. According to the U.S. FDA, the normal dosage amount of vitamin D_3 in prenatal vitamins is 400 international units (IU). This amount of vitamin D_3 in typical prenatal vitamin supplements taken by mothers is not sufficient to provide proper levels to breastfed infants [14,18]. Most multivitamins contain amounts of vitamin D_3 ranging from 50 to 100 IU. The suggested daily intake for children and adults is 600 IU a day and for infants 1,000 IU a day [14,18]. Daily intake of vitamin D_3 is beneficial, however excessive amount of vitamin D_3 can elicit adverse health problems primarily hypercalcemia, kidney failure, and calcification of arteries and soft tissues [18,19].

Current research findings have proposed vitamin D_3 deficiency leads to an increased prevalence of both asthma and food allergies. The aim of our literature review is to evaluate whether an increased supplementation of vitamin D_3 for mothers during pregnancy and while breastfeeding can reduce the risk of asthma and food allergies in children.

Literature Review

Active vitamin D_3 promotes immune tolerance through modulation of antigen presenting cell function, induction of regulatory

T cells, and alteration of the T Helper (Th) cytokine response. Jones et al. [17] conducted a study on infants with high and low levels of vitamin D_3 and exposed the children to food and inhalant allergens. The study revealed children with higher levels of vitamin D_3 had a decreased type 2 helper T cell (Th2) activation. The Th2 cells produce cytokines responsible for allergic disease. The Th2 suppression afforded by vitamin D ultimately decreases the child's risk for developing food allergies and asthma within the first 6 months of life [17].

Several studies have indicated that vitamin D_3 deficiency is linked to the prevalence of asthma and food allergies in children. Bener et al. [22] measured a significant difference ($p < 0.001$) in serum vitamin D_3 levels in asthmatic children (n = 483) compared to a control group of non-asthmatic children (n = 483) [22]. Asthmatic children were selected from the Pediatric Allergy-Immunology Clinics of Hamad General Hospital and non-asthmatic children were selected from the Primary Health Care Clinics in Qatar. These researchers found that a majority of the asthmatic children (68.1%) had deficient serum vitamin D_3 levels (<20.0 ng/mL) suggesting a correlating these two phenomena. Sufficient levels of serum vitamin D_3 (>30 ng/mL) were found in 13.5% of asthmatic children indicating that other non-vitamin D_3 related factors likely contribute to this condition as well. There was a significant difference ($p < 0.001$) in the number of asthmatic children (48.1%) with moderate vitamin D_3 deficiency (10-19 ng/mL) compared to the control group (25.1%). Additionally, there were significantly more ($p < 0.001$) asthmatic children (26.3%) with severe vitamin D_3 deficiency (<10 ng/mL) compared to the control group (11.0%) [22]. Because more asthmatic children were identified as having deficient or moderately deficient vitamin D_3 levels, inadequate vitamin D_3 may result in the development of asthma. These data suggest that vitamin D_3 supplementation may help mitigate the development of asthma.

Baek et al. [23] measured the serum vitamin D_3 levels of infants in association to food allergy sensitization and atopic dermatitis. Researchers found a positive correlation between infant serum vitamin D_3 levels and sensitization to food allergies in this cross-sectional study at the CHA Bundang Hospital in South Korea. Serum vitamin D_3 levels were measured in 130 infants with detected food allergies. Vitamin D_3 levels were compared to each infant's sensitization to food allergens. Serum vitamin D_3 levels were defined as deficient (<20.0 ng/mL), insufficient (20.0-29.0 ng/mL), and sufficient (≥30.0 ng/mL). Sensitization to food allergens were defined as non-sensitized (<1 food allergen), mono-sensitized (1 food allergen), or poly-sensitized (≥2 food allergens) for food specific IgE levels >0.35 kU/L. Significantly more vitamin D_3 deficient (44.6%) infants showed poly-sensitization compared to vitamin D_3 insufficient (29.8%) and sufficient (18.8%) infants, (P=0.001) [23]. These results suggested that vitamin D_3 deficiency is a factor in increased sensitization to food allergens affecting infants.

The incidence of food allergies in infants related to vitamin D_3 deficiency may stem from maternal vitamin D_3 levels during pregnancy. Chiu et al. [24] studied a birth cohort of 164 mothers and their children ages 6 months to 4 years of age. Researchers examined the relationship between maternal vitamin D_3 levels during pregnancy and each child's sensitization to allergens and atopic diseases, including both food allergies and asthma [24]. A significant difference ($p < 0.05$) in allergen and food sensitization was found between the 1.5-year-old and 2-year-old children of mothers that had either deficient or sufficient levels of vitamin D_3 during pregnancy. The 1.5 year-old and 2 year-old children of mothers with deficient vitamin D_3 levels had an increased sensitization to allergens and food compared to children of the same age of mothers with sufficient vitamin D_3 levels. A significantly decreased risk of asthma in the 4-year-old children of vitamin D_3 sufficient mothers (OR 0.22, CI 0.06-0.92; p = 0.038) was found compared to vitamin D_3 deficient mothers. Four year old children with higher levels of vitamin D_3 also showed a significantly decreased risk of asthma (OR 0.18; 95% CI 0.03-1.08; p = 0.061) [24]. The results support low maternal vitamin D_3 levels as a contributing factor in the risk of developing childhood food allergies and asthma.

Due to the high prevalence of asthma and allergies in children, we next wanted to examine studies that investigated the prevalence of vitamin D_3 insufficiency in pregnant women and their neonates [11]. Bodnar et al. [25] conducted a study in the United States to determine the relative risk of Vitamin D_3 insufficiency in black and white pregnant women and their neonates. The pregnant women's serum was tested at 22 weeks gestation, and the neonate's blood was tested after birth. Bodnar et al. found that pregnant women and neonates residing in the northern states were at a higher risk for vitamin D_3 insufficiency due to decreased sunlight exposure, even when taking 400 IU prenatal vitamin D_3 supplement recommended by the U.S. FDA [25]. This study suggests higher vitamin D_3 supplementation is needed to achieve sufficient vitamin D_3 status. To further examine a connection between vitamin D deficiency and asthma/food allergies, future work should focus on determining whether a higher incidence of these diseases occur in children who were born and reside in areas of decreased sunlight exposure.

An additional area of consideration includes whether high dose vitamin D_3 supplementation is safe and effective in improving vitamin D_3 status in pregnant women and their neonates. Hollis et al. [26] considered the safety of increasing prenatal vitamin D_3 supplementation. These authors found that increasing the dosage to 4000 IU in comparison to the previously recommended 400 IU had higher efficacy in achieving sufficient vitamin D_3 status in the pregnant mother. There were no adverse reactions in the high dose supplementation group [26]. Moreover, a separate but similar study conducted in New Zealand found that 4000 IU prenatal supplementation beginning at 27 weeks gestation significantly increased both the mothers and infants vitamin D_3 status to a sufficient level [27]. This study affirmed a new viable treatment to improve the perinatal vitamin D_3 status.

Result and Discussion

This review details the significant linkage between food allergies, asthma, and vitamin D_3 deficiency. Individuals with asthma had significantly lower serum vitamin D_3 levels (both moderately and severely deficient) than compared to those without asthma [22]. Individuals with the lowest level of serum vitamin D_3 also had the highest percentage of poly-sensitization, sensitization to more than one allergen. Moreover, there was a significant link between the mother's serum vitamin D_3 levels and the child's sensitization to food allergies and asthma [23]. Both of these studies show that there is a significant link between vitamin D_3 deficiency and food allergies and asthma.

A majority of the studies that revealed a connection between vitamin D deficiency and food allergies and asthma have taken place in relatively homogenous populations. Therefore, further studies need to be conducted in more heterogeneous populations to further test whether this link still exists amidst increased genetic variability.

Although much of the population is vitamin D_3 insufficient or deficient, the most vulnerable groups are pregnant women and their neonates [19,20]. In this literature review, we detailed research that showed that dietary intake of the daily recommended dose of vitamin D_3 by the United States Food and Drug Administration (400 IU) leads to insufficient quantities of this vitamin in the serum [25]. Moreover, pregnant women must be supplemented with even higher levels of vitamin D_3 in order achieve sufficient levels for themselves as well as for their neonates [26]. Clinical trials have shown that high dose supplementation is safe and without any side effects [27]. In summary, higher doses of vitamin D_3 supplementation is safe and effective in raising serum levels in pregnant women and their neonates.

We propose that high dose supplementation (4000 IU) during pregnancy may reduce the incidence of food allergies and asthma among neonates. Since there is no cure for food allergies and asthma, prevention is the key to stopping this epidemic. Previous research has shown that supplementation reduced asthma and food allergy exacerbations in individuals with these diseases [28]. High dose supplementation is a safe and effective way to increase the serum levels of vitamin D_3 in both pregnant women and their neonates [26]. By increasing the levels in these populations, the prevalence of food allergies and asthma may decrease among the general population in the United States. This literature review warrants future longitudinal cohort studies examining high dose prenatal vitamin D_3 supplementation and long term outcomes of the infants.

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Statement of Ethics

The authors do not make any recommendation for or against the use of vitamin D supplementation to prevent food allergies or asthma. A physician should be consulted regarding nutritional supplementation.

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