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Vitamin D and skin Atopic Diseases

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Abstract

In past years, the use of vitamin D has acquired interest in the treatment of certain common skin disorders such as atopic dermatitis and chronic urticaria. Currently, there are controversial results in the studies carried out and there is no clear indication for systematic preventive or therapeutic use of vitamin D in these skin disorders. In this article we reviewed the effects of prenatal and postnatal preventive use of vitamin D in the development of skin diseases in the newborn such as atopic dermatitis. There is also revised the treatment effect of vitamin D in chronic urticaria, and atopic dermatitis.

Keywords: Immunoglobulin; Atopic dermatitis; Chronic urticaria; Vitamin D; Allergies

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Introduction

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that usually starts in early infancy, but also appears in adult age in few. AD is frequently associated with elevated levels of immunoglobulin E (IgE). Most AD patients have a personal or family history of allergies, such as allergic rhinitis, food allergy or asthma. Chronic urticaria (CU) is a characterized by hives or wheals, which are edematous and pruritic, appearing longer than 6 weeks. Wheals typically last for less than 24 hours and pruritus is the most common associated symptom of CU. CU has been associated to autoimmunity[1] but there is no clear link between CU and atopy[2].

In the past years, the use of vitamin D has acquired interest in the treatment of certain common skin disorders such as AD and CU.

Vitamin D is well known for its major role in the intestinal, skeletal, kidney and parathyroid mechanisms for homeostasis of calcium and phosphorus[3]. Vitamin D metabolism begins through absorption by the skin as vitamin D_3 (cholecalciferol) and absorption through the gut as either vitamin D_2 (ergocalciferol) or vitamin D_3. Cholecalciferol and ergocalciferol are then metabolized in the liver to 25-hydroxyvitamin-D (25(OH)D)[4]. 25(OH)D is subsequently metabolized in the kidney to its active form,1,25-dihydroxyvitamin D (1,25(OH)2D), or calcitriol. 25(OH)D is the major circulating form of vitamin D and reflects synthesis in sun-exposed skin as well as dietary intake. Dietary sources of vitamin D include oily fish and egg yolks, as well as vitamin D fortified milk, but many individual's diets may be lacking in these sources.

Serum 25(OH)D levels of ≥ 50 nmol/L are important for optimal bone health (calcitropic function of vitamin D)[5]. Serum 25(OH)D levels above 30 to 32 ng/mL are required for optimal health. Serum levels between 10 and 30 ng/mL are considered insufficient and levels < 10 ng/mL reflect deficiency. Newborn infant 25(OH)D plasma levels are strongly correlated with maternal levels, indicating that infant vitamin D status is dependent on maternal vitamin D status[6]. Maternal sunlight exposure also influences breast milk vitamin D concentrations[7]. However, breast milk, despite in other benefits, has generally low vitamin D concentrations, with levels of around 25 IU/L in mothers who have normal 25(OH)D levels[8]. Maternal oral vitamin D supplementation during lactation will increase breast milk vitamin D concentrations[9]. Current recommendations for maternal vitamin D intake during lactation (assuming minimal sun exposure) of 400-600 IU/Day appear inadequate[5].

Baiz *et al* established in 2013 the cord blood mean of 25(OH)D level in 44 nmol/L[10]. Although cord blood 25(OH) D levels are highly correlated with infant and maternal serum levels[11,12], it is important to note that levels in cord blood are usually lower than maternal levels[13,14].

Immunomodulatory effects of Vitamin D

Recently, vitamin D has acquired an important role as immunoregulator of biological functions such as: 1) decrease Th1 cytokine production[15]; 2) induce FoxP3+ regulatory T cells, 3) inhibit B lymphocyte function, resulting in reduced IgE secretion; 4) affect the innate immune system via the induction of macrophage production of the antimicrobial peptides β-defensine and cathelicidin activated by toll-like receptors (TLRs) 2 and 4[16]; 5) enhance skin barrier function; 6) inhibit dendritic cells activation and function induced by lipopolysaccharide(LPS); 7) suppress Toll-like receptor production by monocytes, 8) enhance interleukin(IL)-10 production by mast cells and 9) suppression of IL-6 and C-reactive protein (CRP) synthesis[17]. Vitamin D receptors (VDRs) have been identified on nearly all cells of the immune system including T cells, B cells, neutrophils, macrophages, and dendritic cells (DCs)[18]. The vitamin D metabolite 1,25(OH)2D3 ($VitD_3$) has a potent immunosuppressive effect although the exact mechanism underlying remains unclear[19]. Van der Aar studied Treg cell induction after $VitD_3$ priming of 2 distinct skin DC subsets: Langerhans cells (LCs) and dermal dendritic cells (DDCs)[20]. Authors observed that T regulatory cells generated by Vitamin D3-primed LCs were fork head box protein 3 (FOXP3)+ cells, and the T cells developed in response to $VitD_3$-primed DDCs were FOXP3- cells expressing IL-10[20]. Together, these data show that priming DDCs and LCs with $VitD_3$ results in the induction of distinct types of Treg cells. Indeed, peri-natal vitamin D deficiency produced Th2 skewing and reduced IL-10 secreting T regulatory cells[21]. It has been demonstrated that vitamin D inhibits interferon gamma (IFN-γ) production and promotes IL-4, IL-5, and IL-10 production in a mouse model[22]. It seems that vitamin D deficit could stimulate predominant Th2 responses. Moreover, lower vitamin D levels were associated with elevated serum total IgE[23,24]. Therefore, correction of serum concentrations of vitamin D could reduce IgE level.

Table1: Potential immunoregulatory roles of vitamin D[25].

Decreased inflammation	Enhanced defence mechanisms
Inhibits B lymphocyte function and then, IgE secretion	Enhances skin barrier function
Suppress TLR production by monocytes	Induces macrophage production of the antimicrobial peptides β-defensine and cathelicidin activated by toll-like receptors TLRs 2 and 4
Enhances IL-10 production by mast cells	Stimulates natural killers
Inhibits maturation and migration of DCs	
Decreases Th1 cytokine production	
Induces FoxP3+ regulatory T cells	
Stimulates Treg cells	

Prenatal vitamin D preventive effects

Stelmach *et al* did not observed association between cord blood concentration of 25(OH)D and occurrence of the incidence of wheezing, AD, food allergy, during the first two years of life analyzing data from 190 participants[26]. Curiously, authors observed an inversely association between cord serum 25(OH)D levels and multi-triggered wheezing. Another study prospectively demonstrated that increased maternal serum levels of 25(OH)D predisposed infants to AD at 9 months of age[27]. However, there are several studies that suggest that vitamin D deficiency contributes to the development of AD. Rueter *et al* published in 2014 an expert opinion reviewing the impact of in utero and postnatal vitamin D exposure on allergy risk in childhood[28]. Authors concluded that low cord blood 25-hydroxyvitamin D levels may be associated with increased risk of eczema and wheeze but not asthma and allergic rhinitis.

Jones *et al* studied 231 high-risk infants from an Australian prospective birth cohort measuring cord blood 25-hydroxyvitamin D concentration[29]. There was a significant seasonal variation in its concentration suggesting that sunlight exposure was an important determinant. Eczema was significantly more likely in those infants with lower cord blood 25-hydroxyvitamin D concentration but there was a lack of association between cord blood 25-hydroxyvitamin D concentration and allergen sensitization, food allergy and eczema severity. This investigation concluded that reduced vitamin D status in pregnancy, respectively in umbilical cord plasma of the newborn, may be a risk factor for the development of atopic dermatitis in the first year of life. In a prospective study of 596 pregnant women, the children whose mothers had a higher concentration of vitamin D had an increased risk of AD and asthma compared to children whose mothers had a lower concentration of vitamin D[27].

In another study, Miyake *et al* concluded that consumption during pregnancy of food containing vitamin D was protective against symptoms of AD in the first 2 years of life[30]. In UK study of pregnant women by Goldring *et al*[31], a control group (no vitamin D supplementation) was compared with two intervention groups receiving 800 IU/day ergocalciferol or a single bolus of 200.000 IU cholecalciferol. Authors did not observe any differences by 3 years of age in allergic disease outcomes.

Recently, it has been published the WAO recommendation suggesting that clinicians, parents and other decision makers do not use vitamin D supplementation in breastfeeding mothers with the intention of preventing allergic diseases in their children[32].

Postnatal vitamin D preventive effects

Back *et al* observed that higher intake of dietary vitamin D during the first year of life was correlated with an increased risk of eczema but not asthma or allergic rhinitis at age 6 years[33]. Oren *et al*. compared vitamin D deficient patients with vitamin D sufficient patients, and assessed the prevalence of atopic disorders[34]. In these patients, there was an increased risk of AD among those who were vitamin D deficient, although there was no significant difference in the risk of asthma or allergic rhinitis. However, other authors did not observed an association between vitamin D and the AD occurrence but neither between vitamin D and the AD severity[35].

Supplemented vitamin D treatment effects

Some studies have demonstrated an inverse association between vitamin D levels and severity of AD[36,37]. The study determined serum 25(OH)D levels and SCORAD index levels in 37 Italian children. There was an inverse correlation between serum concentrations of 25(OH)D and clinical severity of AD. However, in a Brazilian study of 105 patients with AD younger than 14 years of age, serum vitamin D concentrations were not significantly related to AD severity[38]. Other authors found no statistically significant associations between 25(OH)D serum levels and prevalence or incidence of atopy, AD, asthma or wheezing in adults[39]. In a total of 72 Korean patients with AD, the results showed that serum vitamin D levels were lower in children with AD than in healthy children, but the same relation was not observed between adults with AD and healthy adults[40]. In a case-control study in Hong Kong Chinese children, Vitamin D deficiency was associated with childhood AD and high total IgE. Serum 25(OH)D levels correlated inversely with both long- and short-term AD severity[41], but vitamin D deficiency and insufficiency were prevalent in Hong Kong Chinese children. Other authors did not observed evidence that vitamin D insufficiency/deficiency was an aggravating factor or a comorbidity of AD[42]. Curiously, Mesquita *et al* found higher levels of 25(OH) D in AD patients than in paired controls[43].

There are several studies that have linked vitamin D supplementation with either the decreased risk or clinical improvement of AD. A Japanese study assessed the effect of maternal vitamin D supplementation in lactating mothers of infants who had facial eczema[44]. Authors did not observed differences in infant eczema severity at 3 months and 2 years of age. However, the supplementation group developed more doctor-diagnosed food allergy than the placebo group ($p = 0.03$). Javanbahkt *et al*[45] assessed the potential treatment benefit of vitamin D supplementation in improving AD symptoms, and found that administration of oral vitamin D alone or vitamin D in combination with vitamin E showed a significant improvement in Scoring AD (SCORAD) severity score index when compared to placebo. Other authors detected that vitamin D supplementation may affect the severity of AD, especially in children with allergic sensitization[46]. Some studies showed vitamin D supplementation to be an effective treatment in reducing AD severity[47-49]. Sidbury *et al* evaluated the effect of vitamin D supplementation on AD improvement, and randomly assigned vitamin D or placebo to eleven children with AD[50]. Although there was a beneficial effect in the treatment group, there was no statistically significant change in the mean of either group's AD clinical severity score. The contradictory results in the studies of 25(OH)D levels in patients with atopic dermatitis (AD) in relation to AD severity based on clinical eczema score may be explained by the fact that a single clinical eczema score does not reflect long-term severity and evolution.

Recently, a systematic review and meta-analysis to determine the serum 25(OH)D levels in AD patients compared with those in healthy controls showed that serum vitamin D level was lower in the AD patients and vitamin D supplementation could be a new therapeutic option for AD[51]. Other recent meta-analysis concluded that vitamin D supplementation improves AD and ameliorates it severity, and can be considered as a safe and tolerable therapy[52]. Some studies actually have established a relationship between vitamin D deficit, AD, and skin colonization by *staphylococcus aerus* and *Malassezia furfur*, but vitamin D supplementation could play a major role against these microorganisms in the development of AD and should be considered a treating option[53].

Similarly, several studies report an inverse relationship between vitamin D levels and severity of CU. In 2015, Movahedi *et al* studied one hundred and fourteen patients with CU along with one hundred and eighty seven sex-matched and age-matched healthy volunteers as the control group[54]. Authors detected a significant positive correlation between vitamin D levels and urticaria activity score. This study showed that patients with CU had reduced levels of vitamin D, while vitamin D deficiency could increase susceptibility to CU. Thorp study on 50 adults with CU within a 4-week period (September 2009) showed that vitamin D levels were significantly lower in subjects with CU compared with controls ($p = 0.16$) and the proportion of all subjects with vitamin D deficiency (defined as 25(OH)D < 30 ng/mL) was not significantly different between the 2 groups (CU, 48%, controls 28%)[55]. In a Egyptian study, low vitamin D levels were associated with CU but not with the severity of the disease[56]. However, Chandrashekar *et al* found a negative correlation between the severity of urticaria and serum 25[OH]D levels[57]. Rasool *et al* in a study of 192 subjects with CU[58]. CU patients had lower serum 25(OH)2D levels, and showed elevated response in resolving the symptoms of CU following Vit-D3 supplementation in combination with antihistamine and systemic corticosteroid. T. Goetz *et al* treated 57 CU patients with low vitamin D with 8 to 12 weeks of vitamin D 50.000 IU weekly followed by daily supplementation[59]. 70% had complete resolution of symptoms in a mean of 4.2 weeks. Cutaneous symptoms were classified into three categories: generalized itching without rash, urticaria and angioederma, or rashes of any other type with or without itching. Authors concluded that serological measurement 25(OH)D in patients with idiopathic CU can identify those patients with low vitamin D levels who may improve their Cutaneous symptoms with vitamin D supplementation. Oguz Topal *et al* studied the effects of vitamin D supplementation on the symptoms and quality of life scores in CU and to vitamin D levels in CU patients in comparison with controls[60]. Serum 25(OH)D concentration was significantly lower in CU group compared to healthy subjects ($p < 0.001$). Authors concluded that supplementation with vitamin D may provide improvement in both the severity of symptoms and the quality of life scores in these patients. Similar results were observed in other studies[61]. In a prospective, double-blinded, single-center study, 42 subjects with CU were randomized to high (4,000 IU/d) or low (600 IU/d) vitamin D_3 supplementation for 12 weeks as add-on therapy to standardized triple-drug therapy (cetirizine, ranitidine, and montelukast)[62]. Authors concluded that add-on therapy with high-dose vitamin D_3 (4,000 IU/d) could be considered a safe and potentially beneficial immunomodulators in patients with chronic urticaria. Grzanka *et al* found similar results in 35 patients with active CU when compared to serum 25(OH)D concentration from normal subjects[63] but the study failed to show any effect of vitamin D status on the circulating C reactive protein (CRP) concentration in CU patients. Although more studies are needed, these conclusions suggest that vitamin D deficiency may be a supplementary indicator for autoimmune urticaria[64].

Conclusions

Although, vitamin D status in pregnancy may be an important part of preventive strategies, the available evidence does not allow us to draw firm conclusions on whether either in utero or postnatal vitamin D status affects the risk of allergic disease. Supplementing infants with vitamin D might be also a safe and effective strategy for reducing the risk of asthma and allergic diseases such as AD. Currently, the evidence with regard to the influence of vitamin D status (affected by both diet and lifestyle) on the development of allergic disease is limited and conflicting. It is difficult to determine when low serum vitamin D levels contributed to the development of AD, whether damage of skin from AD led to low vitamin D absorption from the sun, or low serum vitamin D levels and AD are unrelated. The majority of studies have failed to show any consistent associations between 25(OH) D levels and subsequent allergic disease. Anyway, further studies are needed.

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