



Food allergy: the perspectives of prevention using vitamin D

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Purpose of review

We reviewed the scientific publications in the last 2 years on the connections between vitamin D and food allergy, and endeavor to focus on the possible indications for supplementation in order to prevent allergies.

Recent findings

Ecological studies have suggested a possible relationship between sun exposure and atopic diseases such as asthma, atopic dermatitis and anaphylaxis. However, no direct evaluation of vitamin D status has been performed. Recent studies evaluating the relationship with vitamin D levels at birth or during pregnancy have shown conflicting results with the lower levels of vitamin D associated with eczema, the higher with increased food allergy prevalence.

Summary

Although the role of vitamin D in extraskeletal function is certainly intriguing and must not be underestimated, at the moment there is a lack of consistent data addressing the topic of vitamin D supplementation in the prevention of food allergies. However, in light of the vast amount of literature regarding the mechanisms connected with atopic diseases, an evaluation of serum levels of vitamin D and eventually supplementation must be considered as a further opportunity to understand and treat atopic diseases. In this regard, well designed trials on vitamin D supplementation to prevent food allergies are urgently needed.

Keywords

allergies, childhood, food allergy, supplementation, vitamin D

INTRODUCTION

Vitamin D has long been considered essential for bone mineralization, but following the demonstration that every tissue in the human body has vitamin D receptors and that vitamin D has pleiotropic effects, interest in the role of this vitamin/hormone has increased exponentially. This is evident from the number of scientific papers produced in recent years regarding this topic [1]. The best indicator of vitamin D status is considered the assessment of serum 25-hydroxyvitamin D [25(OH)D], which is the main circulating vitamin D metabolite with the most potent biological effects. Indeed, the 25(OH)D levels reflect total vitamin D intake from sunlight exposure, dietary intake and supplements.

Recent attention has been focused on the non-skeletal effects of vitamin D, and epidemiological studies have reported significant associations between the levels of 25(OH)D and the risk of metabolic, neoplastic and immunologic disorders such as

type 1 diabetes, multiple sclerosis and atopic diseases [2].

As 10% of vitamin D is acquired through food ingestion and 90% via synthesis in the skin after exposure to sunlight, several lines of concern have been raised on the achievement of appropriate effective serum levels in humans [2,3]. In fact, in the last few decades, there has been evidence of a worldwide vitamin D deficiency at all ages. This is probably because of a combination of altered eating habits (less consumption of fish liver oil, fish, milk, eggs and margarine), behavioral factors (less time spent outdoors, less exposure to sunlight, clothing coverage for personal or religious reasons) and

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KEY POINTS

- Recent birth cohort studies showed no relationship between vitamin D deficiency and food allergy; the highest levels of vitamin D correlated with the higher risk of food allergy.
- There is a lack of consistent data addressing the topic of vitamin D supplementation to prevent the development of food allergy.
- In light of the vast amount of literature regarding the mechanisms connected with atopic diseases, an evaluation of serum levels of vitamin D and eventual supplementation must be considered a further opportunity to understand and treat atopic diseases.
- Well designed trials on vitamin D supplementation to prevent food allergy are urgently needed.

national campaigns (against exposure and promoted use of sunscreen to prevent skin cancer). We must consider that other intrinsic factors are involved as determinants of vitamin D levels, such as at the individual level the skin melanin content may interfere with vitamin skin production, intestinal absorption of vitamin D may be deficient because of secondary causes like cystic fibrosis or celiac disease may be involved. The risk of lower levels is common in obese individuals and is probably due not only to their lifestyle, but also to take-up in the adipose tissues of this fat-soluble vitamin [4]. Last but not least, vitamin D levels are clearly associated with the intensity of exposure to UVB determined by seasons (lower in winter and higher in summer) and by latitude (inversely with distance from the equator).

On the basis of these premises, vitamin D deficiency (VDD) is an ongoing epidemic not only in the elderly, but also in pregnant and breast-feeding women, in their offspring and in children in general [5[•],6^{••}].

THE POSSIBLE MECHANISMS OF VITAMIN D IN THE DEVELOPMENT OF FOOD ALLERGY

Although there is plenty of evidence of the effects of vitamin D on calcium and bone physiology, in particular its conversion of the prohormone 25(OH)D to the active form 1,25(OH)₂D, it also has effects on epithelial cells, T cells, B cells, macrophages and dendritic cells, orchestrating important responses of the innate and adaptive immunization systems [3[•],7]. All these cells, representative of the immune system, are able to convert the circulating prohormone form into the active form. The innate

response driven by 1,25(OH)₂D is represented by the capability to express antimicrobial peptides, such as cathelicidin, that induces the expression of gene encoding. This action plays a role in maintaining the mucosal integrity and strengthening the physical defense epithelial barrier by stimulating junction genes [8,9]. Nevertheless, the potential effect of vitamin D on Th1/Th2 adaptive immune response is of interest and related to food allergy. Vitamin D receptor agonists have been shown to impact on Th1 and Th2 cell function, suppress allergen-specific IgE synthesis, inhibit dendritic cell maturation and induce tolerogenic dendritic cells, and finally to induce regulatory CD4⁺CD25⁺Foxp3⁺ T cells [10,11]. In-vitro studies [12,13] showed that exposure to 1,25(OH)₂D converts human CD4 T cells into IL-10-secreting Treg cells and suppresses IgE production by human B cells with further elaboration of tolerizing and anti-inflammatory cytokines.

The potential mechanisms for the hypothesized link between VDD and food allergy in children were studied by Vassallo and Camargo [14], who hypothesized that the hormone deficiency at a particular time, such as the postnatal period, can increase the susceptibility to colonization by abnormal intestinal microbial flora, that contributes to increased intestinal permeability, which in turn leads to excessive and inappropriate exposure of the immune system to dietary allergens. In particular, in the case of VDD, there could be an immune system imbalance at the intestinal level that compromises immune tolerance and increases the susceptibility to infection, which acts by destroying the normal epithelial barriers [14]. It is also possible that VDD contributes to cutaneous food allergen sensitization as transcutaneous sensitization could be relevant, particularly in children presenting VDD [15]. It is possible to speculate that reduced antimicrobial factors and the presence of noneffective tight junctions by VDD at the skin level may determine an abnormal exposure/stimulation of the immune system, leading to eczema, allergic sensitization and development of food allergy [15], accompanied by a significant increase in the severity of atopic dermatitis [16].

VITAMIN D DEFICIENCY: A RISK FACTOR FOR FOOD ALLERGY?

The topic regarding VDD as a risk factor for childhood asthma has recently been reviewed by Litonjua [17^{••}] who pointed out how vitamin D may affect asthma and allergy through the different mechanisms mentioned above, which include the development of the lung and immune systems.

Regarding the probable association between VDD and food allergy, from a historical point of view, the first reports came from the observations of geographic variations in cases of anaphylaxis and epinephrine autoinjector prescription rates in the United States and Australia, and related to latitude [18–23]. There were more cases and more prescriptions in the less sunny regions of both countries, independently of demographic factors, and more frequently in pediatric patients. These findings raised the possibility of a causative role of sunlight or vitamin D status in food allergy. It was further confirmed by a consistent inverse relationship between increasing latitude and proxy markers of food allergy prevalence, such as epinephrine prescriptions and food-allergy-related hospital admissions [21,23,24,25[¶]], as well as infant hypoallergenic formula prescription rates [26] in less sunny regions. Evidence was produced in different countries showing also a relationship between season of birth (fall and winter, the less sunny months) and food allergy prevalence (food sensitization and doctor-diagnosed food allergy) [25[¶]].

Furthermore, a large population survey [National Health And Nutrition Examination Survey (NHANES 2005–2006)] showed that VDD was associated with higher levels of specific IgE and therefore allergic sensitization to various allergens, both food and environmental, in children and adolescents, but not in adults [27]. This was reinforced by the findings of higher rates of food sensitization in infants born to mothers with low vitamin D intake during pregnancy [28]. Interestingly, in the NHANES study [27], the lower levels of 25(OH)D were also associated with clear risk factors like black or Hispanic race/ethnicity, a low socioeconomic status, TV or computer use for more than 4 h a day, less milk drinking and not taking vitamin D supplementation. These epidemiological data failed to show the nonlinear, U-shaped association between low and high vitamin D levels with the increased serum IgE levels observed in some previous studies [29,30]. Interestingly, in the NHANES study, the authors did not find enough participants with high 25(OH)D levels to confirm the previous reports, which led to considering once again that VDD is extremely common, at least at particular latitudes.

At that time, the researchers' interest focused on the early phases of life, considering pregnancy and the perinatal period as crucial times when different factors, including VDD, may act synergistically to influence the immune system and initiate allergic sensitization.

In a study [31] that measured vitamin D levels in cord blood and aeroallergen sensitization in a 5-year

follow-up, both low and high levels of cord blood 25(OH)D were associated with increased allergic sensitization, confirming a U-shaped association. The study was conducted in Tucson, Arizona, where the climate offers a unique setting for studying high exposure to vitamin D from sunlight. On the contrary, in a birth cohort study, Liu *et al.* [32] reported no overall association between cord blood vitamin D levels and food-specific IgE.

Interestingly, in the last year, three studies were published that specifically focused on the relationship between vitamin D levels at birth or during pregnancy, allergic sensitization and food allergy. These studies tried to evaluate the direct relationship between early childhood vitamin D status and development of food allergy. In a pilot study, Mullins *et al.* [33[¶]] evaluated the differences in the neonatal levels of vitamin D and compared the levels of peanut allergy in children below 6 months of age with birth-matched controls. They found that the relationship between neonatal 25(OH)D levels and childhood peanut allergy was nonlinear with slightly higher levels (75–99.9 nmol/l) associated with lower risk than those in the reference group. The risk of peanut allergy at the lower levels of neonatal vitamin D, levels present in very few children of this cohort, was not significantly different from the reference group.

In another study from Australia, Jones *et al.* [34^{¶¶}] evaluated the relationship between cord blood 25(OH)D₃ and eczema, allergic sensitization and food allergy at 12 months of age. Lower concentrations were highly prevalent in this high-risk allergy Australian cohort, with only 24% of participants having adequate vitamin D concentrations (≥ 75 nmol/l). The lowest vitamin D levels at birth (< 50 nmol/l) were associated with an increased risk of eczema at 12 months, but no significant difference between IgE-associated and non-IgE-associated eczema was observed. The authors found in this high-risk group a high rate of allergen sensitization (21%) and IgE-mediated food allergy cases (10.4%) after the first year of life, but the risk of developing IgE-mediated food allergy was not related to cord blood 25(OH)D₃ [34^{¶¶}]. The authors concluded that this effect together with the data confirming efficacy on viral-induced wheezing [35] appears to be independent of IgE-related features, which raises questions about the real mechanisms involved.

Finally, a very recent study [36^{¶¶}] from Germany directly addressed the effects of maternal and newborn vitamin D status and their impact on food allergy development in the offspring. 25(OH)D was measured in blood samples from mother–child pairs during pregnancy and at birth, and correlated with atopic manifestations in the first 2 years of life.

The authors found a high correlation between maternal and cord blood 25(OH)D₃ levels, both showing a clear seasonal distribution. Both 25(OH)D₃ highest levels were positively associated with the risk of children presenting food allergy in the first 2 years of life; the highest maternal 25(OH)D₃ levels resulted in a higher risk for sensitization against food allergens [36[■]]. Furthermore, the cord blood regulatory T-cell numbers were negatively correlated with the levels of cord blood 25(OH)D₃, which could be considered a potential contributing mechanism for allergy development. Therefore, the study's message was the demonstration that high vitamin D levels in pregnancy and at birth may contribute to a higher risk of food allergy and therefore that no supplementation is required to protect against allergy.

EVIDENCE FROM SUPPLEMENTATION STUDIES

Because it is clear that VDD may begin in pregnancy, prevention of the effects of VDD must include the prenatal period. Vitamin D deficiency and insufficiency are prevalent year-round among pregnant women, especially in those with darker skin [37]. Vitamin D supplementation for pregnant women is debated and was the subject of a recent Cochrane review that showed that single-dose or continued-dose supplementation during pregnancy increases the vitamin D concentrations, as measured as 25(OH)D at term [38[■]]. The authors pointed out that, even though the existing supplementation guidelines should be supported, the clinical significance of improving the vitamin levels and the potential use of this intervention strategy as part of the routine prenatal care are yet to be determined because the number of trials and outcomes is too limited to draw conclusions on efficacy and safety [38[■]]. Furthermore, the outcomes investigated so far have been concerned mainly with the safety of pregnant woman and newborns, without giving any evidence of effective prevention by vitamin D supplementation against diseases later in life [38[■]].

Other issues continue to be debated. The definition of optimum serum levels and the levels that indicate vitamin D deficiency or insufficiency are not globally recognized, being rather defined for osseous outcomes but not for global health effects [2,3[■]]. Low levels of vitamin D have been commonly observed among healthy newborns [34[■],39] and at other pediatric ages [27]. They are independently associated with several easily identified factors (seasonality, maternal levels and intake, diet,

supplements and skin color) and reinforce the debate on the advantages of providing supplementation during childhood. In fact, a crucial point for any vitamin D intervention concerns dosages. Current daily recommended doses for children [40] are designed for the beneficial effects on muscle and skeletal function, but probably not for the immune system response to allergens or infections [1[■]]. In infants with serum 25(OH)D levels less than 50nmol/l, a vitamin D supplementation intake of 400IU daily did not always achieve the optimal levels [41[■],42[■]]. However, further work is needed to determine the exact dose to safely meet the target levels without overcorrection, particularly if we could prevent the development of immune-mediated diseases.

THE PERSPECTIVES

Currently, there is a lack of consistent data addressing the association between the VDD and the development of food allergy, determined by the findings from the most recent birth cohort studies [33[■],34[■],36[■]]. Indeed, more studies have shown an association among vitamin D and allergic diseases, but definitive clinical supplementation trials are lacking. Further knowledge is necessary to provide more evidence and this can derive only from vitamin D supplementation-controlled studies. There are currently several ongoing clinical trials (clinicaltrials.gov identifiers: NCT00856947 and NCT00920621) on vitamin D supplementation during pregnancy and the onset of allergic diseases in the offspring that would help to address our practice, but the results will only be available within a couple of years [43,44]. However, these ongoing studies consider the development of asthma and allergic sensitization as their main endpoints, but not food allergy, which is the focal point of this review. We stress the need for supplementation effect studies on the development of food allergy.

In the meantime, we should consider that all the previous shown evidence and demonstrations could help us to evaluate the opportunity for vitamin D supplementation in pregnant women and children, keeping in mind that there is more evidence for the positive effects of supplementation. It is also very important in this regard to remember Liu *et al.*'s [32] report that VDD may increase the risk of food allergy and sensitization among individuals with certain genotypes. As mentioned above, the authors found that VDD was not associated with food allergy when examined alone. On the contrary, VDD was significantly correlated with specific gene polymorphisms, providing evidence of gene–vitamin D interaction on food allergy [32].

CONCLUSION

In conclusion, evidence of the association among vitamin D and development of food allergy is rather scarce and conflicting. Possible positive correlations come from ecological studies associating sunlight exposure to food allergies. However, recent studies have shown that the higher levels of vitamin D may increase the risk of food allergy and allergic sensitization. The role of vitamin D in extraskeletal function is certainly intriguing and must not be underestimated. In light of the vast amount of literature regarding the mechanisms, demonstrated *in vitro* and *in vivo*, connecting the vitamin D levels to the development of allergic diseases, eczema and infections, we must consider this hormone as a further opportunity to understand and treat atopic diseases. For this reason, well designed trials on vitamin D supplementation are needed, particularly concerning food allergy, in order to give more strength and evidence to the hypothesis that vitamin D could really contribute to the prevention strategy.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 319).

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