
Asthma and Allergy “Epidemic” and the Role of Vitamin D Deficiency

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Abstract

The increase in asthma and allergies prevalence that has been recorded in many countries during the last decades, and the reemergence of vitamin D (VD) deficiency in many populations worldwide, renders fairly plausible the assumption of an underlying association between these two conditions and justifies the research effort invented in this issue. Indeed, there is growing body of evidence from epidemiological, laboratory, and clinical studies, suggesting that such an association does exist. The hypothesis of low levels of VD leading to compromised fetal programming and impairment of various immune functions involved in asthma and allergic disorders, stands as the most credible explanation of this presumed association. However, the evidence is not yet definite and there are some conflicting results among studies. As a consequence, no safe conclusions can be drawn yet, and more research is required in order to fully clarify the involvement of VD deficiency in the pathogenesis of asthma and allergies, and decide if VD has a role to play in the prevention and therapy of these disorders.

Keywords

Allergies • Asthma • Epidemic • Fetus programming • Vitamin D • VD supplementation

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14.1 Introduction

Vitamin D (VD) has gained much attention in recent years and is considered a topic of great scientific interest. Research on VD was in the past decades focused mainly on the osseous-related endocrine system and skeletal health [52]. However, it has now become common knowledge that essentially all tissues bear vitamin D receptors (VDRs) and, in addition, a wealth of evidence supports the vitamin's immunomodulatory role regarding both the innate and adaptive components of the immune system [34]. This, in turn, has led researchers to seek associations between VD deficiency states and a number of immune mediated illnesses, including autoimmune, atopic and infectious conditions. Indeed, there are fairly compelling evidence supporting potential roles of VD deficiency in the pathogenesis of a wide spectrum of mainly chronic and phenomenally unrelated illnesses such as, cardiovascular, autoimmune, respiratory and allergic disorders, metabolic syndrome, dementia, and cancer [38, 95].

The importance of VD can be further emphasized by the fact that in modern societies VD deficiency tends to become a common health problem, probably because of lifestyle changes, such as the more sedentary way of life with more time spend indoors, and the increased use of sun safety practices [52].

The purpose of this chapter is to examine the current evidence for the potential role of VD deficiency on asthma and other allergic disorders focusing mainly on food allergy (FA) and atopic dermatitis (AD).

14.2 Vitamin D Sources and Metabolism

In humans, the majority of VD is synthesized in the skin under the influence of ultraviolet solar radiation which converts 7-dehydrocholesterol into cholecalciferol (vitamin D₃). Sunscreens and clothing prevent the conversion of 7-dehydrocholesterol to vitamin D₃ [34]. Apart from D₃ there is also another bioactive, plant-derived form of VD, named vitamin D₂ (ergocal-

ciferol), which has been produced commercially since the early 1920s and is now widely used for food fortification and as a dietary supplement. Structurally, the two forms are similar, with vitamin D₂ having an extra methyl group on carbon 24 and an additional double bond between carbons 22 and 23. However, these structural differences have no major consequences on the metabolic activation of VD, and so the two forms are still officially regarded as being equivalent [102]. Dietary VD is only a minor contributor to overall VD used by human organisms, and the exact amount depends on each individual's particular diet. In general however, food sources of VD are limited and include oily fish, cod liver oil, and egg yolks. Fortification of infant formula with VD is mandatory whereas, some dairy products are also fortified with VD. The dietary intake is more important when sunshine exposure is inadequate. People in northern countries are dependent on dietary sources to ensure adequate VD levels, especially during the winter months.

VD is not biologically active and must be converted to its active form. To achieve this, VD from either the skin or the diet, enters the circulation where it is transported by the vitamin D binding protein (DBP) to the liver where it is metabolized to 25 hydroxyvitamin D (25(OH)D; calcidiol) by the enzyme vitamin D 25-hydroxylase. 25(OH)D is the major form of circulating VD; nevertheless, it is practically biologically inactive. 25(OH)D is further transported through DBP to the kidneys where it goes through another hydroxylation in the kidney's mitochondria by the enzyme 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) resulting in 1,25(OH)₂D (calcitriol) which is the actual active form of VD. Once formed, 1,25(OH)₂D can interact with the specific nuclear VDR to exert its actions.

Kidneys were long thought to be the only organs capable to produce calcitriol. However, we now know that expression of 1-OHase is widespread in extrarenal sites and the conversion of calcidiol to calcitriol can take place in many tissues other than kidneys, such as skeletal and heart muscle, T and B lymphocytes, macrophages, liver, brain, placenta, breast, colon, prostate, and bronchi [12]. It has to be mentioned that

VD is not, strictly speaking, a vitamin but rather a hormone, since vitamins are substances that cannot be synthesized in sufficient quantities by an organism, and must be obtained from its diet.

14.3 Vitamin D Deficiency

14.3.1 Definition of Vitamin D Deficiency

There is a continuing debate on how VD deficiency is defined. Serum concentration of 25(OH)D is considered the best determinant of VD status. However, determining 25(OH)D serum concentrations is not straightforward and considerable interassay discrepancies have been noted in studies comparing different commercially available 25(OH)D tests [25, 114]. In addition to the previous technical problem, there is also scarcity of data regarding the correlation between 25(OH)D serum concentrations with health outcomes, something that makes the definition of VD deficiency on the basis solely of 25(OH)D levels quite challenging. On the other hand, calcitriol is not useful as a marker of VD status or for the correlation with health outcomes because of its short serum half-life [17]. Furthermore, it has been demonstrated that polymorphisms in DBP gene may affect the percentage of bioavailable VD making the issue of determining the normal levels of 25(OH)D even more complicated [96]. Given the many uncertainties, a scientific advisory committee in United Kingdom concluded that the current data are insufficient to clarify relations among VD intake, biochemical status, and chronic disease outcomes [109].

However, despite the many unanswered questions, most authors use 25(OH)D serum levels of 50 nmol/l (25 nmol/l = 10 ng/ml), as the cut-off value of VD deficiency, although, some recommend higher levels, e.g. higher than 75 or even 100 nmol/l [52, 102]. The 2011 report from the Institute of Medicine Committee on dietary requirements for calcium and VD levels concluded that according to available evidence, VD concentration of 20 ng/ml (50 nmol/liter) is adequate for the needs of at least 97.5% of the popu-

lation [102]. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) has recently re-established the recommendation of a 25(OH)D concentration > 50 nmol/l to indicate sufficiency whereas, severe VD deficiency during childhood, is defined as 25(OH)D concentrations <25 nmol/l [17]. In other pediatric guidelines [81], VD status has been given a more detailed definition and has been schematically divided in 4 categories, as follows: severe deficiency: <12.5 nmol/L (5 ng/mL); deficiency: 12.5–37.5 nmol/L (5–15 ng/mL); insufficiency: 37.5–50 nmol/L (15–20 ng/mL); sufficiency: > 50 nmol/L (20 ng/ml).

14.3.2 Determinants of Hypovitaminosis D

The main determinants of VD status is time spend indoors and sunshine exposure, skin pigmentation, clothing, use of sunscreen, nutrition and use of VD supplements [17]. It has been demonstrated that serum levels of 25(OH)D are not always a characteristic of people living in sun deprived areas. VD levels tend to be higher in Northern than in Southern Europe [123]. This phenomenally "odd" conclusion has been confirmed by subsequent multicenter studies that used a single laboratory for their measurements and the comparison of 25(OH)D levels was straightforward ([67, 74] [122]). The high serum levels of 25(OH)D in Norway and Sweden are probably due to a high intake of fatty fish and cod liver oil, whereas the lower serum 25(OH)D in Spain, Italy and Greece may be the result of more pigmented skin and sun avoidance practices [123].

Obesity has been associated with low serum levels of VD [81], although the underlying mechanism has not still verified. It may occur because of trapping of VD in fat cells [98] or, on the other hand, VD deficiency may not be a consequence but rather a risk factor and obesity may predispose to VD deficiency through upregulation of adiponectin synthesis [115]. Secondary causes of VD deficiency are medications (e.g. rifampicin, anticonvulsants), and diseases causing malabsorption such as celiac disease and cystic fibrosis [78].

14.3.3 Epidemiology of Vitamin D Deficiency

Regardless of the thresholds used, VD deficiency unambiguously comprises a common health problem worldwide. Epidemiological studies suggest that approximately 50% of adults and children worldwide are VD deficient, with serum concentrations of 25(OH)D below 50 nmol/L [13, 73]. Hilger et al., in a recent comprehensive systematic review of the literature, found that 88.1% of the papers reported mean or median values of 25(OH)D levels below 75 nmol/l, 37.3% below 50 nmol/l and 6.7% below 25 nmol/l [51]. Studies included in this review contained data on almost 170,000 participants from 44 countries, representing practically all geographic areas of the earth. The authors found significant differences between the various geographic areas, with values being significantly higher in North America than in Europe or Middle East/Africa region. Age-related differences were not found in Europe and North America. However, in the Asia/Pacific region, children and adolescents had significantly lower 25(OH)D values compared to adults and elderly. In contrast, children and adolescents from Middle East and Africa had significantly higher values than adults and elderly. No significant sex-related differences were observed in any of the regions, although reports in women tended to show lower 25(OH)D values, especially in the Asia/Pacific and Middle East/Africa regions [122]. The later observation could be, at least partially, explained by limited sun exposure of women due to cultural practices.

14.4 Asthma and Allergies: An Epidemic of Modernity?

14.4.1 Epidemiological Evidence

The prevalence of asthma has been increasing since the decade of 1960s in most areas of the world [132]. The highest prevalence of the disease has been observed in developed countries [9]. In 2006, Eder et al. summarized data from

registries and epidemiological surveillance studies, and found that increases in the prevalence of asthma had been reported from most of the countries during the second half of the twentieth century. However, this apparent global increase in asthma prevalence was evident only up to the 1990s, whereas after then the temporal pattern was not clear. In some populations, the prevalence of asthma was still rising, while on the contrary in others appeared to be stable or decreasing slightly. In particular, in some areas of the Western world, the prevalence seemed to have reached a plateau [40].

In the same year, another group published a study [5] on global trends in the prevalence of asthma, rhinoconjunctivitis, and eczema in childhood. Researchers repeatedly collected cross-sectional data for two age-groups of school children – 6–7 years and 13–14 years – from many countries as part of phase 3 International Study of Asthma and Allergies in Childhood (ISAAC) and compared data with that of a baseline survey that had been undertaken approximately 7 years before. A large number of centers from around the world took part in this study. In the majority of centers there was a change in prevalence of 1 or more standard errors for at least one disorder, with increases being twice as common as decreases, and increases being more common in the 6–7 year age-group than in the 13–14 year age-group. An exception was observed for asthma symptoms in the older age-group, where decreases were more common at high prevalence. For both age-groups, more centers showed increases in all three disorders more often than showing decreases, but most centers had mixed changes. The changes were greatest for eczema in the younger age group, and for allergic rhinoconjunctivitis in both age-groups.

The ISAAC study also found an increase in AD in both age groups. There was a significant increase in the prevalence of AD, ranging from 0.07 to 1.09% in 48 countries with decrease in 8 countries and little change in 12 countries in the 6–7-year age group and increase in 47 countries, decrease in 32 countries, and little change in 26 countries in the 13–14-year age group. In general, the increase occurred primarily in previous

areas of low prevalence, whereas the areas with previous high levels showed leveling off [116].

The prevalence of FA is difficult to be determined with precision because standard criteria for its definition are still lacking. Two recent systematic reviews estimated that FA roughly affects 0.1–6.0% of the European population [90] and more than 1–2% but less than 10% worldwide [26]. In US, from 1997 to 2007, the prevalence of reported FA increased by 18% in children less than 18 years old [18]. Despite the absence of an accurate estimation of its prevalence, available data suggest that there has been a significant increase in the last two decades and the problem has reached almost epidemic characteristics in developed western countries [10, 91, 113, 125]. FA is considered now the main cause of anaphylaxis [72].

14.4.2 Hypotheses for Explaining the “Epidemic” of Asthma and Allergies

Although much research effort has been investigated in the explanation of increasing prevalence of asthma and allergies, a comprehensive and explicit model to interpret this phenomenon is still lacking. The majority of authors try to approach and explain this issue based on the hygiene hypothesis [117] which suggests that children living in modern families of westernized societies have minimal exposure to infectious agents in the first years of life, which in turn leads to inappropriate development of their immune system and its regulatory pathways. As a consequence, the transition from a prevalent Th2 to a balanced Th1/Th2 response that ensues during infancy is not properly and fully implemented, and children develop a propensity for asthma and allergies [101]. However, despite favorable evidence from experimental studies, epidemiological data have not been consistent and sufficient to confirm this hypothesis, and now it is evident that this model cannot explain on its own the many dimensions of the extensive asthma and allergy epidemic [99].

In 2007, Litonjua and Weiss proposed a new approach to explain the issue, based on another consequence of westernized way of living. They argued that, as populations become more prosperous they tend to spend more time indoors and expose themselves less to sunlight [76]. This results in VD deficiency that can lead in a disposition for the development of asthma and allergies. VD deficiency’s harmful effect begins as early as prenatal life through its impact on fetal lung and immune system development [64], and is continued postnatally. This hypothesis offers a reasonable alternative explanation for some of the epidemiologic attributes related with the asthma epidemic, namely the increased risks associated with obesity, and recent immigrants to westernized countries. Some of the cons and pros of this theory will be reviewed in the next pages.

14.5 Is Vitamin D a Key Player Allergy and Asthma Epidemic?

14.5.1 The Regulatory Role of Vitamin D in the Immune System

The concept of VD possessing a key role in the regulation of the immune response has emerged from the discovery of a variety of immune cells, such as antigen-presenting cells, natural killer cells, and B and T lymphocytes, that express the intracellular VDR and are responsive to 1,25(OH)₂D [36]. Moreover, it is supported by the ability of various types of immune cells, including peripheral blood mononuclear cells, activated T lymphocytes, dendritic cells, and quiescent CD4 cells, to convert 25(OH)D to 1,25(OH)₂D [1, 79, 110]. A number of studies have demonstrated the modulatory effects of VD in the function of cells involved in numerous aspects of immunity, affecting both innate and adaptive immunity.

The immune and inflammatory processes that underlie allergic and asthmatic disorders are

complex and still not fully understood; however, there is robust evidence that impaired immune regulation plays a pivotal role in the pathogenesis of these disorders [77]. Based on these grounds, it has been argued that VD is directly involved in the pathogenesis of asthma and allergies, and indeed, there is a substantial body of high-quality research in favor of this connection. Some of the evidence supporting a potential role of VD deficiency in the development of asthma and allergies through defective immunoregulation are reviewed below.

Calcitriol decreases the maturation of dendritic cells (DC) and their ability to activate T lymphocytes. Activation of VDR signaling pathways inhibits DC maturation as evidenced by decreased levels of DC markers, such as MHC-class II, co-stimulatory molecules (CD40, CD80, and CD86), and other maturation-induced surface antigens (e.g. CD83) ([8]). Similarly to DC, the antigen-presenting and T cell stimulatory ability of monocytes and macrophages is reduced upon exposure to $1,25(\text{OH})_2\text{D}$ [4, 8]. Immunomodulatory pathways involve both direct and indirect effects on the proliferation, differentiation, and function of T cells. VD administration decreases TH1 cytokine secretion and inhibits T-cell proliferation [60, 86]. Matheu et al. found that VD administration in mice could induce IL-4, IL-5, and IL-13 ([80]). A study on naive human cord CD4 and CD8 T cells showed that VD exerts an inhibitory effect on IFN- γ production induced by IL-12, and suppresses IL-4, and IL-13 expression induced by IL-4 [36]. VD stimulates $\text{CD4}^+\text{CD25}^+\text{Foxp3}^+$ Treg cells to increase the secretion of IL-10, which is considered a chief effector molecule in VD-mediated promotion of the immunosuppressive states of T cells [106]. Activation of VDR modulates the humoral immune response by inhibiting IgE expression in B cells and enhancing IL-10 expression [48, 50]. Apart from IL-10, it has been recently demonstrated that $1,25(\text{OH})_2\text{D}$ has a profound inhibitory effect on the development of human Th9, a CD4^+ T cell subset that is highly associated with asthma, in an IL-10 independent manner [119]. In a study that examined the effects of VD on T cell differentiation it was found that

the stimulation of $\text{CD4}^+ \text{CD25}^-$ T cells in the presence of $1,25(\text{OH})_2\text{D}$ inhibits the production of pro-inflammatory cytokines including IFN- γ , IL-17, and IL-21, and stimulates expression of high levels of CTLA-4 and FoxP3. CTLA-4 plays an important role in the suppressive activity of Treg, whereas FoxP3 $^+$ Treg cells have a central role in the prevention of catastrophic autoimmunity. Through the previous pathway, T cells treated with $1,25(\text{OH})_2\text{D}$ were able to suppress proliferation of normally responsive T cells, indicating that they possessed characteristics of adaptive Tregs [59]. In patients with severe asthma, there was a strong correlation of low serum concentrations of $25(\text{OH})\text{D}$ with a paucity of FoxP3 $^+$ Treg cells in the peripheral blood. In the same study it was also found that the frequency of circulating FoxP3 $^+$ Treg cells were significantly lower in steroid resistant than in steroid sensitive asthmatic patients with comparable disease severity [27]. Effector CD8^+ T cells convert from IFN- γ^+ (Th1) to IL-13 $^+$ (Th2) cells as a result of their activation by IL-4-producing CD4^+ T cells, a process having been related with the development of asthma [66]. It was also recently shown, that the addition of $25(\text{OH})_2\text{D}$ during CD8^+ T-cell differentiation prevents IL-4-induced functional conversion of CD8^+ T cells from IFN γ to IL-13 producing cells, via a mechanistic link to CYP11A1 activity [108].

VD also regulates the effectiveness of innate immunity in antimicrobial defense mechanisms [83]). This is mainly accomplished through the induction in skin, lung, and monocytes of cathelicidin [47, 107], an antimicrobial peptide that has a pivotal role in the host defence against various microbial infections [44, 88]. Apart from that, VD can augment skin defence mechanisms by increasing locally the production of some other antimicrobial peptides, such as b-defensin 2 and b-defensin 3, epidermal lipid synthesis enzymes, fatty acid synthase, serine C-palmitoyltransferase, and 3-hydroxy-3-methylglutaryl-coenzyme A, as well as the structural proteins of corneocytes, filaggrin and involucrin [53]. All of the above are essential elements for the development of structural and functional integrity of skin.

In general, however, despite the abundance of available data on the immunomodulatory effects of VD and the quite a few proposed mechanisms [62], the synthesis of evidence into a coherent model that can clearly explain how these effects can intervene in the propensity of an individual to develop asthma and allergies has not yet become feasible.

14.5.2 Vitamin D and Asthma

There is an ongoing debate in medical literature as to whether VD deficiency has a causal association with the development of asthma and allergies. Most of the epidemiological and pathophysiological data support the existence of such a link, although there have been contradictory results too [23, 24, 42, 57, 133]. A lot of studies from different geographic areas have shown high prevalence of VD deficiency in asthmatic children. VD insufficiency was very common in North American children with mild-to-moderate persistent asthma and furthermore, the low levels of VD were associated with higher odds of severe exacerbation [20]. In another population-based study it was shown that low serum concentrations of 25(OH)D, were strongly correlated with reduced spirometric indices (FEV₁, and FVC) [14]. A study conducted in Costarican children, demonstrated that VD levels were negatively associated with airway responsiveness, eosinophil counts, IgE levels, and likelihood of hospitalization for asthma exacerbations [19]. In two studies from Italy, low levels of VD in children were associated with reduced lung function and increased reactivity to exercise; only 11% of children with asthma had adequate VD levels [31, 32]. A study from Turkey in preschool aged children found that the frequency of VD deficiency and insufficiency was higher in children with asthma, compared to the controls [120]. An Indian study showed that, compared with controls, children with asthma had lower 25(OH)D concentrations and proportion of Treg cells, whereas the proportions of B cells with IgE receptors (CD23 and CD21) were higher [28]. In a randomized, double-blind,

placebo-controlled trial, the daily supplementation with 800 IU of VD, in addition to standard therapy, for 2 months in schoolchildren from Japan with asthma resulted in significant improvement in levels of asthma control [118].

Contrary to the previous results, however, some other studies indicated that supplementation with VD has no effect in asthma. So, in a double-blind, randomized, placebo-controlled trial in Irish children with uncontrolled asthma, the authors assessed the effect of 15 weeks of a relatively high dose of VD supplementation (2000 IU/day) on subjective asthma symptoms, lung function, and biomarkers of inflammation/allergy. They found that apart from decreased school days missed, VD supplementation failed to demonstrate any advantageous changes in asthma parameters [63]. Likewise, a recent meta-analysis found only relatively weak evidence to support VD supplementation for the reduction of asthma exacerbations, and no real evidence to support any benefits of VD supplementation for other asthma-related outcomes in children [100].

A number of hypotheses have been postulated to explain the possible pathogenetic link between asthma and VD deficiency. One of these hypotheses is based on the protective role of VD against infections with the reasoning being as follows: Viral respiratory tract infections (VRTI) are the most common trigger of asthmatic exacerbations, especially in children, and typically lead to more severe symptoms compared to non-asthmatics [56]. VD has virucidal effects [22, 39, 121] and, in addition, may also exert antiviral effects through alterations in growth and differentiation of airway epithelial cells [21]. Considering the above, it is plausible that VD deficiency may weaken the defense mechanisms against respiratory infections and thus indirectly increase asthma exacerbations and morbidity [16].

Evidence exists for an association between low maternal VD levels during pregnancy and increased risk of wheezing or asthma. In three observational studies from USA, Japan, and Scotland, it was shown that maternal VD supplementation protects offspring from the development of wheeze [23, 24, 37, 82]. In another large prospective cohort study, low levels of 25(OH)D

at birth – but not in mid-gestation – were associated with a higher airway resistance measured at the age of 6 years [45]. These results may indicate that VD deficiency could affect the programming of the developing lung resulting in increased disease susceptibility [35, 69]. In support of this assumption there are findings from genetic studies demonstrating regulatory effects of $1,25(\text{OH})_2\text{D}$ in airway smooth muscle genes related with morphogenesis, cell growth, and survival, as well as genes encoding structural proteins; all these genes are known to be involved in airway remodelling [11, 15]. These results were strengthened by consistent findings from a study which showed that VD-regulated genes were markedly over-represented in developing human lung transcriptomes; a significant number of these genes were known to be associated with asthma susceptibility [64]. The aforementioned studies support a genomic mechanistic pathway linking low levels of maternal VD with childhood asthma susceptibility, possibly through fetal programming. However, it has to be mentioned, that two recent randomized controlled studies that aimed to investigate the effect of VD supplementation during pregnancy (beyond the usually recommended doses) on asthma-like symptoms in the first 3 years of offspring life, resulted in inconclusive findings [30, 75]. Although, the authors of both trials acknowledge that their studies may have been underpowered to detect a potentially important clinical effect, the results underline the complexity of the issue and the fact that is far from being considered adequately answered [126].

VD, apart from being involved in the pathogenesis of asthma, it may also affect the response to treatment by enhancing the therapeutic response to corticosteroids. Searing et al. showed that in asthmatic children decreased serum VD levels were associated with increased corticosteroid use; the observed correlation may be due to either more severe disease in children with low levels of VD, or to the signaling effects of VD on corticosteroids pathways [111]. Goleva et al. showed that both steroid requirements and in vitro steroid responsiveness were negatively

associated with VD status in children; the same trend was also observed in adult patients though it did not reach statistical significance. The later may suggest that the effects of VD were stronger in childhood asthmatics, probably because of the less advanced airway remodeling [46]. The molecular mechanism of steroid resistance is not yet clear but a well-known characteristic of steroid-resistant (SR) asthmatic patients is the inability of their CD4 T cells to increase IL-10 synthesis after in vitro stimulation with corticosteroids [49]. Xystrakis et al. demonstrated that the addition of $1,25(\text{OH})_2\text{D}$ and dexamethasone to cultures of CD4 T cells from SR asthmatics, enhanced IL-10 secretion to levels comparable with those produced from cells of steroid-sensitive patients treated only with dexamethasone. They further showed that supplementation with VD of SR asthmatic patients, reversed steroid resistance through induction of IL-10-secreting Tregs [134]. Zhang and colleagues went further and showed that VD could also enhance the anti-inflammatory action of corticosteroids in an IL-10 independent manner through the induction of mitogen-activated protein kinase phosphatase-1 (MKP-1) in blood monocytes. However, they also observed that the responses in patients with SR asthma remained significantly lower compared with patients with steroid-sensitive asthma [135, 136]. In a recent study, Lan et al. showed that pre-treatment of patients with VD enhanced the dexamethasone-induced nuclear translocation of glucocorticoid receptors in airway epithelial cell cultures and monocytes of VD deficient adult patients with severe asthma exacerbations. They also showed that supplemental VD ameliorated the oxidative stress and increased the clinical response to corticosteroid. Their results indicate that VD-deficiency aggravates the oxidative changes observed in severe asthma exacerbation and also imply a possible role for VD therapy in acute asthma [71].

To summarise, although many aspects of the underlying mechanism still remain obscure, there is plethora of data suggesting an aetiological association between VD deficiency and asthma.

14.5.3 Vitamin D and Food Allergy

Epidemiological data have linked FA with sunlight exposure by showing that FA is more prevalent in regions further away from the equator [84, 85]. A recent study from Korea compared VD serum levels and the incidence of food induced anaphylaxis (FIA) between 2 regions of high and low solar radiation; VD levels were lower and concurrently FIA incidence was higher in the region with the lower solar radiation [65]. This kind of studies can lead to assumptions but cannot prove that FA is correlated to VD status and not to any other sunlight-derived, seasonal and/or geographic factor. However, they have provided a stimulating framework for further research on the subject [104]. Indeed, the research hypothesis of a connection between VD and FA has been largely corroborated by cross-sectional and cohort studies assessing VD dietary intake during pregnancy, or measuring maternal, cord blood, neonatal or childhood VD status. Sharief et al. used a large nationally representative sample from United States of more than 3000 children and adolescent, and found that VD deficiency was associated with allergic sensitization to selected foods. This association was not observed in the adult group of the study [112]. Similarly, in a cross-sectional study from Korea that included 226 infants with atopic dermatitis or FA it was found that VD deficiency increased the risk of food allergen sensitization [7]. In another large prospective cohort study conducted in Australia, infants with 25(OH)D < 50 nmol/l at 12 months of age were more likely to suffer from challenge-proven FA – especially to egg and peanut – and were more likely to have multiple food allergies compared with those with adequate VD levels [3]. Interestingly, this association was evident only among infants of Australian-born parents, suggesting a gene–environmental interaction [94].

Nwaru BI et al. showed that maternal intake of VD during pregnancy was associated with decreased risk of food sensitization in the offspring at the age of 5 years [89]. Chiu CY et al. demonstrated an inverse association between cord blood 25(OH)D levels from a birth cohort of

Taiwanese children and milk sensitization at the age of 2 years [33]. However, there are also studies that failed to find a valid association between cord blood 25(OH)D levels and FA [29, 61]. Though not proving an association does not necessarily rule out its existence, their results have introduced some scepticism. What is more, a German study reported that maternal and cord blood 25(OH)D was positively associated with children's risk for FA within the first 2 years of life. As a general comment, one could say that the presence of conflicting results reflects the gaps in our knowledge on the exact role of VD in the development of FA.

A proposed model of the induction of FA focuses on the actions of VD on the gastrointestinal tract which is the mucosal site with the richest antigenic exposure in the body. According to this model, VD deficiency not only compromises immune tolerance, but also increases susceptibility to infections and affects gut microbiota composition. The ensuing gastrointestinal infections compromise barrier permeability and other defence mechanisms against dietary and microbial antigens in the intestinal mucosa. These defects synergistically promote dysfunctional responses to food antigens that may manifest as FA in genetically susceptible subjects [124].

14.5.4 Vitamin D and Atopic Dermatitis

AD is characterised by defective skin barrier, skin inflammation, and increased susceptibility to certain skin infections. Given the aforementioned attributes of VD, namely immunomodulatory effects, cathelicidin induction, and impact on the development of skin barrier, it comes as no surprise that VD deficiency is now considered one of the contributing factors in the pathogenesis of AD and indeed, there are many epidemiological reports that have described this association [70, 82, 129, 130]. Besides, there is also direct evidence relating low blood levels of VD in children with the severity of AD [2, 41, 93]. In a large cohort study that sought to examine the associations between early-life VD levels and the

development of eczema and other allergy-related outcomes in a population of black and white children from the same region, it was shown that prenatal 25(OH)D levels were inversely associated with eczema. This association was stronger in white children implying that VD plays a role of varying importance depending on other risk factors present in a subject [127]. In another cohort study of children with a family history of allergic disease, cord blood 25(OH)D concentrations found to be negatively associated with risk of eczema in early childhood [92]. A recent meta-analysis demonstrated that maternal VD status during pregnancy was associated with childhood eczema [128]. Some authors have even suggested that VD supplementation should be included in the therapeutic armamentarium of atopic dermatitis [58, 105].

14.6 Can Vitamin D Increase the Risk of Asthma and Allergies?

Despite the amount of literature supporting a direct relation of VD deficiency with the development of asthma and allergies, there are also quite a few studies suggesting that VD promotes the development of these disorders. Some of the existing antilogy has already been presented herein and some more will be reviewed below.

In a number of studies, VD supplementation has been linked to allergy and asthma [6, 43, 55, 68]. In an elegant review of the literature on this particular topic, Wjst has sited the evidence and discussed the reasoning underlying the findings [131]. As he postulates, the explanation of the apparent paradox of both VD deficiency and VD supplementation promoting asthma/allergy should be sought in the epigenetic programming in pregnancy and early infancy, where both low and high levels of VD lead to the same end result. In cases of excessive VD exposure in newborn period, either by extra supplements or as an additive to baby foods, it is assumed that different reactions can be induced. The kind of reactions depends on how low or rich the intrauterine environment was in VD. This assumption is based on

existing evidence for other disorders showing that their development can be facilitated by large discrepancies between the environments experienced in utero, in early infancy, and later life [131].

Evidence also exists that high VD levels can increase the risk for asthma and allergies independently of dietary supplementation. Hyppönen et al. showed that IgE concentrations were higher in subjects having either low (<25 nmol/L) or very high (>135 nmol/L) levels of 25(OH)D [54]. Rothers et al. demonstrated that both lower (<10 ng/mL) and higher (≥ 20 ng/mL) levels of cord blood 25(OH)D were associated with higher frequency of sensitization to aero-allergens up to the age of 5 years, compared with a reference group (10–19.9 nmol/L) [103]. A Canadian study found that children with both low (≤ 49 nm/L) and high (≥ 75 nm/L) 25(OH)D levels had increased risk of asthma [87]. The above results suggest that possibly a U-shaped association between VD levels and asthma/allergies exists, and that there is a threshold in both low and high 25(OH)D levels associated with increased risk of these disorders.

Finally on his chapter on environmental factors and inflammatory non-communicable diseases, Prescott tried to address the complexity of the issue with an alternative but very interesting approach; he proposed that VD might actually be a proxy for UV exposure, which could somehow reduce a subject's propensity for inflammation. If that was the case, then VD supplementation would not be enough to overcome the effects of a UV deficiency [97].

14.7 Conclusion

The worldwide epidemic proportions of asthma and other allergic disorders and hypovitaminosis D, have been the subject of extensive research efforts in the last two decades. In an attempt to explain the coexistence of these two synchronous “epidemics”, it was proposed that there is a causal link between VD deficiency and the development of asthma and allergies. In support of this is the vast amount of available data showing the

important role of VD in regulation of inflammation and modulation of various immune responses. Indeed, most of the studies have verified the hypothesis of VD deficiency predisposing to the development of asthma and allergies. However, there have been some studies with opposing results, supporting that VD supplements and high VD levels may have a detrimental effect on asthma and allergies. It is undoubtedly very challenging to try to interpret phenomenically discordant results and propose a unifying model. And not surprisingly, despite the bulk of available evidence, there are still huge gaps in our knowledge to allow a translation of basic research on immunomodulatory attributes of VD into clinical practice. Clearly, more research, and especially adequately powered randomised control trials are needed in order to extract safe conclusions on the role of VD in the prevention and treatment of asthma and the other allergic disorders. Up to then, it would be prudent in cases of difficult asthma or recalcitrant eczema, to check VD levels and, if low, to supplement with VD.

Conflict of Interest Authors declare no conflicts of interest.

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