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REVIEW

Vitamin D and allergies

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Abstract: An increasing amount of evidence has established that the biologically active form of vitamin D, 1,25-dihydroxyvitamin D₃, possesses immunoregulatory properties. Vitamin D exerts its effects through binding to the nuclear vitamin D receptor (VDR), which is expressed by cells of the immune system. Most of the immunological effects mediated by vitamin D–VDR are regulatory, inhibiting adaptive immune responses. It has become apparent that the incidence of vitamin D insufficiency is surprisingly high in the general population. A link between low vitamin D serum levels and the increased prevalence of allergic diseases has been proposed. This possible connection was investigated in numerous studies on associations between vitamin D serum concentrations and different allergic conditions, as well as studies on the effect of vitamin D supplementation. Although there is some evidence for a protective role of vitamin D in asthma, no consensus on the role of vitamin D in allergic disease has yet been reached. Still, treatment strategies involving vitamin D supplementation to risk groups, combinatorial corticosteroid and vitamin D treatment in asthma and vitamin D as an immunomodulator in allergen-specific immunotherapy show promise for the future.

Keywords: vitamin D; allergy; immunomodulator.

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1. BIOSYNTHESIS AND MODE OF ACTION

Vitamin D is generated in the human body during exposure to sunlight. Only a minor proportion is normally obtained through diet, *e.g.*, from oily fish species and vitamin D supplemented food products.¹ UVB radiation converts 7-dehydrocholesterol in the skin into pre-vitamin D₃, which after isomerization is converted to cholecalciferol. After transport to the liver, cholecalciferol is hydroxylated by 25-hydroxylase to form 25-hydroxyvitamin D₃ (calcidiol), which is the main circulating form of vitamin D. To generate the biologically active form of vitamin D, *i.e.*, 1,25-dihydroxy vitamin D₃ or calcitriol, 25-hydroxyvitamin D₃ is subjected to hydroxylation by 1 α -hydroxylase (CYP27B1).^{2,3} This second hydroxylation step mainly occurs in the kidney, but CYP27B1 is also expressed in a number of other tissues (Fig. 1). Both vitamin D₂ (ergocalciferol) and vitamin D₃ are used as vitamin D supplements.⁴ Assays analyzing serum vitamin D levels measure 25-hydroxyvitamin D, including 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃.⁴ Hereafter, the term “vitamin D” will be used for both biologically active calcitriol and when referring to supplementation or serum levels of vitamin D.

The biological effect of vitamin D is mediated by the nuclear vitamin D receptor (VDR). The VDR belongs to the nuclear hormone receptor superfamily and is expressed in most tissues of the body. When vitamin D binds to VDR, the receptor dimerizes with the retinoic X receptor (RXR) and the complex activates transcription of genes through interaction with VDR-responsive elements (VDRE) in the promoter regions of these genes.^{2,5,6} A couple of thousand target genes have been found to respond to vitamin D/VDR activation.⁷ Vitamin D plays a well-established role in calcium-phosphate homeostasis and bone metabolism, not least evident by the skeletal symptoms seen in rickets and osteomalacia caused by vitamin D deficiency. However, as indicated by the widespread expression of both CYP27B1 and VDR, vitamin D has several “non-classical” effects in addition to its role in calcium metabolism. These non-classical functions of vitamin D include regulation of hormone secretion, cellular proliferation and cell differentiation.³ Vitamin D also exerts immunomodulatory effects.^{5,8,9}

2. VITAMIN D AND THE IMMUNE SYSTEM

One clear indication that vitamin D might play a role in the regulation of immune responses comes from the observations that cells of the immune system express VDR and respond to vitamin D. Thus, *e.g.*, monocytes,¹⁰ dendritic cells (DC)¹¹ and T-cells^{12,13} express the VDR, and VDREs are found in genes important for immune regulation, *e.g.*, FOXP3,¹⁴ IL-10,¹⁵ and CD14.¹⁶ Another observation indicating a possible role of vitamin D in immune regulation is the increased prevalence of cancer, allergic and autoimmune diseases coinciding with an increasing prevalence of life style related vitamin D insufficiency.¹⁷ Moreover,

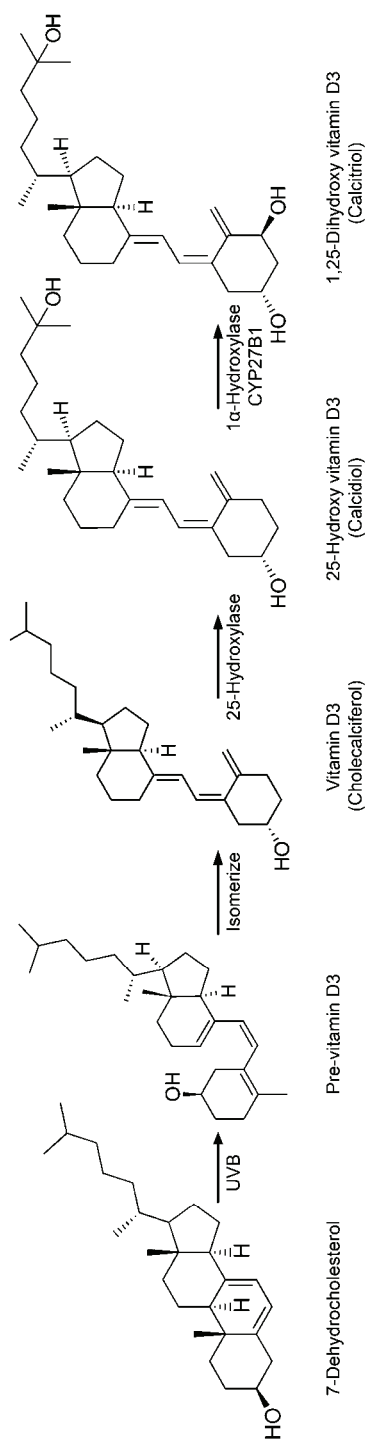


Fig. 1. Metabolic activation of vitamin D. Conversion of 7-dehydrocholesterol to vitamin D3 occurs in the skin, conversion from vitamin D3 to 25-hydroxyvitamin D3 occurs in the liver and the biologically active 1,25-dihydroxyvitamin D3 is produced in the kidney and other tissues, including cells of the immune system.

genetic polymorphisms in the VDR gene have been linked to immune and inflammatory conditions such as Crohn's disease,¹⁸ tuberculosis¹⁹ and asthma.^{20,21}

Vitamin D can affect both innate and adaptive immunity.²² Cells of importance for the innate response to pathogens, *e.g.*, macrophages and epithelial cells, are able to produce locally active vitamin D as they express CYP27B, and to respond to vitamin D through their expression of VDR.^{23–25} Furthermore, vitamin D promotes the synthesis of the antimicrobial peptide cathelicidin, which is part of the innate response to pathogens,^{26,27} and induces autophagy in macrophages, important for the clearance of intracellular pathogens.^{28,29} Innate responses may be negatively regulated by vitamin D through the down-regulation of pathogen pattern-recognition receptors, such as Toll-like receptors (TLR), and suppression of TLR-mediated inflammation.³⁰ If vitamin D seems to have both activating and regulatory effects on the innate immune response, the effect on adaptive immunity is mainly regulatory. Vitamin D may limit adaptive immune responses through its suppressive action on DCs. Several studies showed that vitamin D inhibits the differentiation and maturation of DCs by down-regulation of co-stimulatory molecules and reduces the production of pro-inflammatory cytokines.^{31–33} When cultured with vitamin D *in vitro*, tolerogenic DCs are generated, *i.e.*, the DCs adopt an immature phenotype and produce lower levels of IL-12 and enhanced levels of IL-10.^{34,35} Such tolerogenic DCs are able to promote regulatory T-cell (Treg) responses.^{31,36,37} It was also shown that vitamin D alone or in combination with dexamethasone induces Tregs.^{38–41} Although the promoting effect of vitamin D on regulatory T cell responses is well established, the data on vitamin D's effects on Th2 responses are contradictory. A Th2 promoting effect was suggested by data showing that both Th1 and Th17 responses are inhibited by vitamin D.^{42–46} Moreover, vitamin D was shown to enhance the development of Th2 cells from naïve T-cells in mice.⁴⁷ On the other hand, by its ability to induce Tregs, as discussed above, vitamin D can inhibit Th2 responses. A mechanism involving decreased expression of OX40 and increased expression of TGF- β by DCs that reduces the Th2 response has been described.⁴⁸ Taken together, the pronounced effect of vitamin D on immune regulation suggests that vitamin D insufficiency may play a role in allergic disease.

3. VITAMIN D IN ALLERGIC DISEASE

Allergic disorders are caused by an imbalanced immune response elicited against allergens, which results in a Th2 skewed response and allergic inflammation. Depending on the target tissue for allergen exposure, the allergy may manifest as rhinoconjunctivitis or allergic asthma to inhalant allergens, eczema to food- or contact allergens, gastrointestinal/systemic symptoms to ingested food allergens and systemic reactions to injected allergens. The prevalence of allergic diseases has increased considerably during the last decades.⁴⁹ One explanatory

model for this increase is the hygiene hypothesis, stating that a reduced microbial burden due to improved hygiene in modern society leads to a hypersensitive immune system and increased risk of developing allergy.⁵⁰ The modern Westernized life style also implies changed diet and less time spent outdoors, factors that influence the vitamin D status. Indeed, it has been reported that a large proportion of the population in modern societies has vitamin D serum levels corresponding to deficiency or insufficiency. In a study on a US pediatric population, 9 % of the examined children and adolescents were vitamin D deficient (defined as $<15 \text{ ng ml}^{-1}$) and as many as 61 % were considered vitamin D insufficient ($15\text{--}29 \text{ ng ml}^{-1}$).⁵¹ In an adult British population, approximately 15 % had vitamin D serum levels $<25 \text{ nmol L}^{-1}$ (considered to correspond to vitamin D deficiency) during the winter–spring season.¹⁷ There is no consensus regarding cut-off levels for vitamin D deficiency and insufficiency but recent US guidelines have proposed vitamin D levels above 20 ng mL^{-1} to be considered as vitamin D sufficiency.⁵² It should be noted that guidelines for vitamin D serum levels are based on bone health and that consistent clinical/epidemiologic data on optimal levels for beneficial effects on non-musculoskeletal health are lacking. Still, it was suggested already in 1999 that there may be a link between the nutritional intake of vitamin D and allergies.⁵³ Since then many studies have investigated the relationship between vitamin D and allergy. In a review from 2012, Reinholz *et al.* presented a table of clinical studies on vitamin D in allergic disease.⁵⁴ Eighteen of the listed studies suggested a protective role of vitamin D, six a deleterious role and two studies reported no role for vitamin D in allergic disease. These studies represent populations of various ages and geographic locations, patients with different allergic manifestations as well as subjects with no allergic diagnosis, different means of determining vitamin D status and heterogenic study designs. Taken together, these factors illustrate the difficulties encountered to reach a consensus regarding the role of vitamin D in allergy. The complexity is exemplified below, where some of the studies are discussed.

One may divide studies investigating the role of vitamin D in allergy into two main categories. In association studies, vitamin D serum levels are linked to the incidence of allergic disease. Supplementation studies investigate the effect of vitamin D supplementation, given prenatal (maternal supplementation) or postnatal, on allergic status later in childhood or adult life. In 45 years old subjects from a British cohort, low ($<25 \text{ nmol L}^{-1}$) and high levels ($>135 \text{ nmol L}^{-1}$) of serum vitamin D correlated with higher IgE serum concentrations compared to “normal” vitamin D levels.⁵⁵ No correlation was found between vitamin D serum levels and total IgE levels in a Chinese population with recently diagnosed asthma. However, it was shown that vitamin D insufficiency was prevalent in the same population and that vitamin D status correlated with lung function.⁵⁶ The relationship between lung function and vitamin D serum levels was examined in

14,091 subjects, 20 years or older, participating in a cross-sectional study conducted in the US. The subjects underwent spirometry and serum vitamin D concentrations were determined. In this study, a strong positive relationship was found between serum vitamin D levels and lung function measured as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).⁵⁷ In contrast, in another case-controlled study on adult patients with asthma and controls performed in the UK, no association between vitamin D and asthma severity or lung function could be found.⁵⁸ These studies were all conducted on adults and vitamin D status may be of more importance at an early age during the development of the immune system. Camargo *et al.* analyzed maternal intake of vitamin D during pregnancy and correlated it to recurrent wheeze at three-year age in a prospective pre-birth cohort study in the US.⁵⁹ In this study, a higher maternal intake of vitamin D resulted in lower prevalence of recurrent wheeze, which is a predictor of asthma. A study performed on children in Costa Rica showed that 28 % of asthmatic children exhibited vitamin D deficiency or insufficiency ($< 30 \text{ ng mL}^{-1}$) despite living at a latitude with high sun exposure. Several disease markers, such as total serum IgE, eosinophil count, hospitalization for asthma, anti-inflammatory medication and airway hyper-responsiveness, inversely correlated with vitamin D serum concentrations in this study population.⁶⁰

Vitamin D supplementation has been examined in relation to allergic disease. A couple of studies on children who received oral vitamin D supplementation reported an increased risk for the development of allergic disease in childhood or later in life.^{61–63} Vitamin D supplementation may nonetheless be beneficial by reducing the risk of respiratory infections and, consequently, lowering the risk of asthma exacerbations. This was recently shown in a randomized placebo-controlled trial on school children in Japan.⁶⁴ Children receiving vitamin D supplementation during December–March had a reduced incidence of influenza A infections compared to those receiving placebo. In a subgroup of children with asthma, exacerbations were less common in the vitamin D supplemented group.

4. VITAMIN D IN EXPERIMENTAL MODELS OF ALLERGY AND ASTHMA

To understand better the mechanisms of how vitamin D may affect allergy, murine experimental models have been employed. In these models, mice are sensitized with a model allergen to evoke an allergic Th2 skewed immune response, followed by allergen challenge in the airways. The allergic immune response, allergic inflammation and airway hyper-reactivity are then investigated. Data obtained from VDR knockout mice (VDR KO) indicated that vitamin D might play a deleterious role in allergy and asthma. The VDR KO mice failed to develop airway inflammation and airway hyper-reactivity after chicken albumin (OVA) sensitization, despite high IgE levels and Th2 cytokine production.^{65,66} It

should be noted that in this experimental model, vitamin D treatment did not affect airway inflammation or hyper-reactivity in sensitized wild type mice. In contrast, Topilski *et al.* applied a mouse model for OVA-induced experimental asthma, in which they could show that pretreatment with intraperitoneally (i.p.) administered vitamin D reduced the eosinophilic airway inflammation and IL-4 levels in the bronchoalveolar lavage fluid (BALF) of sensitized mice. Treatment after sensitization but before airway challenge with OVA also significantly reduced the airway inflammation, but to less extent compared to vitamin D given prior to sensitization.⁶⁷ Another study using an OVA model demonstrated an increased allergen induced Th2 profile but a decreased inflammatory response detected in the BALF of mice treated with vitamin D before and during the sensitization and allergen challenge protocol.⁶⁸ These results from experimental models suggest that vitamin D may have dual effects on the allergen specific Th2 response and allergen-induced airway inflammation.

5. VITAMIN D AS A POSSIBLE THERAPEUTIC TOOL IN ALLERGY AND ASTHMA

The results reported by Topilski *et al.* indicate that it is possible to decrease the allergic airway inflammation by vitamin D treatment in previously sensitized mice with an established Th2 skewed allergen specific immune response.⁶⁷ The concept to use vitamin D as an immunomodulator in allergy treatment was further explored by Taher *et al.*⁶⁹ Mice sensitized to OVA were treated with OVA alone or in combination with vitamin D prior to airway challenge with OVA. Co-administration of vitamin D with OVA significantly inhibited the airway hyper-responsiveness and potentiated the OVA treatment effect by increasing the reduction of serum OVA-specific IgE levels, airway eosinophilia and Th2-related cytokines. The treatment-potentiating effect of vitamin D seemed to be mediated by the immunoregulatory cytokines IL-10 and TGF- β , since the levels of these cytokines were elevated in the vitamin D-treated mice and the treatment effect was abrogated in the presence of antibodies to these cytokines.⁶⁹ A similar concept was tested in a mouse model for cat allergy.⁷⁰ In this study, the major cat allergen Fel d 1 was covalently linked to vitamin D and treatment of Fel d 1 sensitized mice with the Fel d 1-vitamin D vaccine was compared to treatment with Fel d 1 alone. Both treatments decreased allergen-specific IgE, Th2 cytokines in the BALF, airway eosinophilia and airway hyper-responsiveness, and in addition generated Fel d 1-specific IgG. The Fel d 1-vitamin D vaccine was more potent than Fel d 1 alone in inhibiting the allergen-challenge induced airway symptoms, especially the eosinophilic inflammation.⁷⁰ Both these studies present promising strategies for improving the current allergen specific immunotherapy by combining an allergy vaccine with vitamin D. The concept of covalently linking vitamin D directly or indirectly to an allergen is particularly interesting as it might enhance the efficacy of the immune modulation,

but it is a challenge to produce stable vaccine formulations with preserved vitamin D biological activity.

Vitamin D was demonstrated to enhance dexamethasone stimulated IL-10 synthesis in human CD4⁺ T-cells.³⁸ Interestingly, vitamin D was able to restore the lost ability of T-cells from patients with steroid-refractory asthma to respond to dexamethasone by IL-10 production *ex vivo*.³⁹ Three patients with steroid-refractory asthma were given oral vitamin D and peripheral blood cells were collected before and after treatment. *In vitro* stimulation of the cells in the presence of dexamethasone showed that vitamin D treatment enhanced steroid responsiveness and led to increased production of IL-10.³⁹ The data suggest that vitamin D could potentially restore the therapeutic effect of glucocorticoids in patients with steroid-resistant asthma.

6. CONCLUDING REMARKS

An increasing amount of evidence points to an important regulatory role for vitamin D in innate and adaptive immunity. The current data suggest that vitamin D may have a beneficial effect on asthma, while the influence on the allergic immune response remains unclear. Carefully designed long-term interventional studies with vitamin D supplementation are required to elucidate further the role of vitamin D in allergy. Still, treatment strategies involving vitamin D supplementation to risk groups, combinatorial corticosteroid and vitamin D treatment in asthma and vitamin D as an immunomodulator in allergen specific immunotherapy show promise for the future.

ИЗВОД

ВИТАМИН Д И АЛЕРГИЈЕ

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Све је више података да биолошки активна форма витамина Д, 1,25-дихидрокси-витамина Д₃, има имунорегулаторне особине. Витамин Д свој ефекат испољава након везивања за рецептор за витамин Д у једру (VDR), који је експримиран у ћелијама имуног система. Већина имунолошких ефеката посредованих витамином Д–VDR су регулаторни, инхибирајући адаптивни имуни одговор. Међу становништвом је изненађујуће велика заступљеност недостатка витамина Д. Има показатеља да постоји веза између мале концентрације витамина Д у серуму и алергијских болести. У бројним студијама је испитивана могућа веза између серумске концентрације витамина Д и различитих алергијских стања, као и ефекат узимања витамина Д. Иако постоје подаци о заштитној улози витамина Д у астми, нема општег става о улози витамина Д у алергијским болестима. Употреба витамина Д код ризичних група, комбинована терапија кортикостероидима и витамином Д код астме, као и употреба витамина Д као имуномодулатора у алерген-специфичној имунотерапији, обећавајући су терапеутски правци.

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