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# VITAMIN D AND ASTHMA

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**ABSTRACT**

The main source of Vitamin D comes from the bioconversion of 7-dehydrocholesterol to cholecalciferol, however, our level of sun exposure has been drastically reduced during the last decades, so it is not unusual to find a high Vitamin D deficiency among the population. There is evidence to suggest that a deficiency in Vitamin D could be associated with a worse evolution of asthma and a greater risk of serious exacerbations. Prenatal Vitamin D supplementation for pregnant mothers could possibly reduce the risk of wheezing and asthma in their offspring, and supplementation intake for asthmatic children could improve the evolution of the disease.

**Key words: Vitamin D, childhood asthma, wheezing, asthma severity, prenatal supplementation, postnatal supplementation.**

## INTRODUCTION

For the past ten years there has been a growing interest in the relationship between Vitamin D (VD) levels with recurrent wheezing, asthma (1), allergy (2), inflammation (3) and immunity (4, 5). In recent reviews about the treatment of asthmatic patients, VD deficiency is already mentioned as one of the factors to be controlled for optimal disease management (6,7,8).

VD exists in the form of VD2 or ergocalciferol, present in plants and fortification supplements, and VD3 or cholecalciferol, whose main source is the cutaneous bioconversion of 7-dehydrocholesterol to cholecalciferol, which occurs in the presence of sunlight. There are also animal sources such as fatty fish (tuna, salmon and mackerel) and beef liver, in addition to supplements that have as an ingredient skim milk, butter, complementary food program products and cereals. Minor sources of VD are cheese, egg yolks and mushrooms. VD undergoes a first hepatic hydroxylation (25-OH-VD) and a second enzymatic hydroxylation at the renal level and in several other tissues (1,25- (OH) 2-RV) (Fig 1) (9)

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## VITAMIN D's MULTIPHACETIC ROLE

Currently, VD is not just considered a type of nutrient, but rather a hormone. Its classic role that is known is its participation in calcium metabolism and homeostasis and therefore in bone health. However, it also participates in the expression of hundreds of genes (9,10) and its deficiency influences the genesis or evolution of many diseases (Table 1):

- Regulates cell differentiation and growth, establishing a relationship in this area between VD deficiency and different types of cancer (11).

- It is a powerful modulator of the immune response, since there are VD receptors in different cell types, such as regulatory T cells, antigen presenting cells, dendritic cells and macrophages, acting as true nuclear receptors of steroid hormones and regulating gene transcription associated with inflammatory response and immunomodulation (12,13). This explains the relationship between VD deficiency and Type I Diabetes Mellitus, Multiple sclerosis, Rheumatoid arthritis, Lupus Erythematosus and Parkinson's disease (14), among others, and the greater severity that a viral infection can achieve in the face of VD deficiency (15,16).

**Figure 1.** Metabolism and sources of Vitamin D.

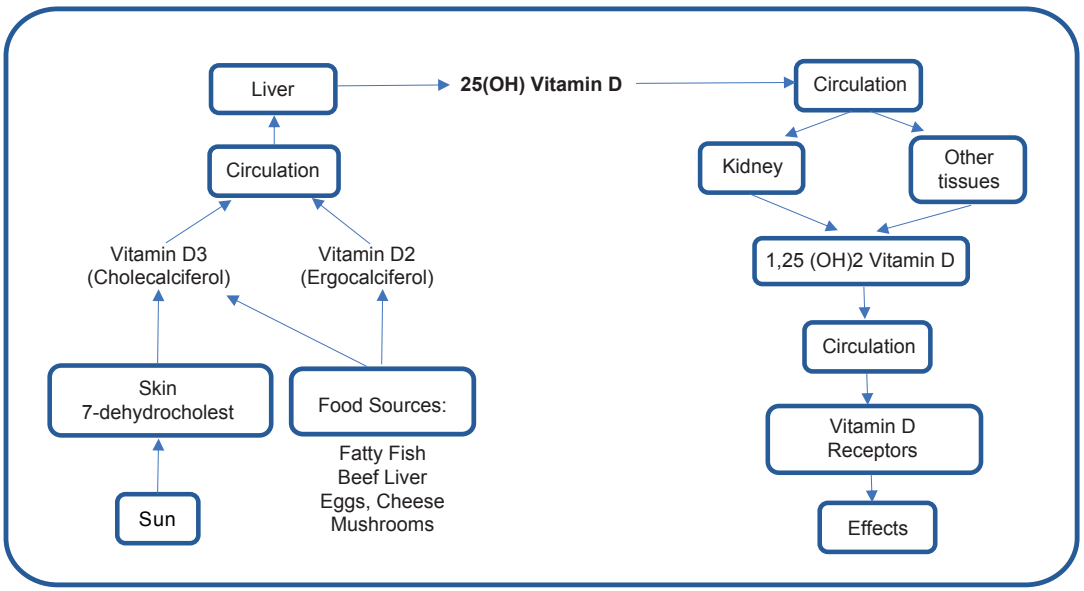


**Table 1.** Extra-skeletal effects of Vitamin D and the consequences of its deficiency.

| Action Mechanism | Effect | Risks of VD Deficiency |
|---|---|---|
| **Regulates differentiation and cell growth, promotes intercellular junctions and reduces angiogenesis** | antineoplastic | Colo-rectal cancer, breast cancer, prostate cancer and other types of cancer |
| **VD receptor is present in most cells of the immune system, reducing its activity and production of autoimmune antibodies** | Immunomodulator | Type I diabetes, Multiple sclerosis, Rheumatoid Arthritis, Autoimmune thyroiditis, Crohn's Disease, Parkinson's Disease |
| **Facilitates signaling of Toll-Like receptors, stimulating synthesis of cathelicidin and other anti-infective peptides** | Promotes Innate Immunity | Viral and bacterial infections |
| **Inhibits proinflammatory cytokines, stimulates anti-inflammatory IL-10 and reduces oxidative stress** | Anti-inflammatory | Asthma, worse asthmatic follow-ups, greater resistance to corticosteroids, greater severity of viral infections. |
| **Inhibits proliferation of vascular smooth muscle cells, inhibits myocardial cell hypertrophy, protects the endothelium** | Cardiovascular protection | Acute myocardial infarction Vascular accidents |
| **Reduces the production of Renin** | Regulates blood pressure | Arterial hypertension |
| **Improves beta cell function in the pancreas Improves insulin sensitivity and glucose absorption in peripheral tissues** | Regulates metabolism | Metabolic syndrome |

VD: vitamin D

- Facilitates the signaling of Toll-like receptors, stimulating the synthesis of cathelicidin, the human antimicrobial peptide LL-37 that participates in the innate immunity of the respiratory system and also of other sites such as skin (17).

- In the airway, VD inhibits pro-inflammatory cytokines, with effect on CD4, IL-2, IL-17 T lymphocytes, Gamma Interferon-induced chemokines, tumor necrosis factor and macrophages and stimulates the action of regulatory T lymphocytes by increasing IL-10 secretion with a potent anti-inflammatory effect (18,19). On the other hand, VD reduces oxidative stress and the production of reactive O2 species (20), which explains why its deficiency is associated with worse asthmatic monitoring and greater resistance to inhaled corticosteroids in these patients.

Pfeffer, in an in vitro study of bronchial epithelial cells of healthy and asthmatic volunteers (21), stimulated these cells with particulate material in the presence or absence of 1.25- (OH) 2- VD, observing the production of proinflammatory cytokines after 24 hours of cell culture. The expression of 510 genes was involved and in 49 of them, the presence of VD regulated its expression, suppressing IL6, the CXCL-10 and IL24 chemokine, both in healthy and asthmatic ones and reduced oxidative stress by promoting the antioxidant pathway of the G6PD gene, which in turn reduces the synthesis of 8-Isoprostane.

## EPIDEMIOLOGY OF HYPOVITAMINOSIS D

There is a high prevalence of VD deficiency in the world. A systematic review by Hilger (22) that included 195 states in 44 countries, with 168,000 individuals found a deficiency, defined as values of 25-OH-DV <20 ng / ml, in 37.3% and insufficient values (<30 ng / ml) in 88.1%. In our country, a national health survey conducted in 2016-2017 showed a severe deficiency in 13% of women aged 15-49 and insufficient levels at 84% (23). Brinkmann (24) studied 108 children in Punta Arenas (39% eutrophic, 46% overweight and 15% obese), finding 62% with severe deficiencies (<12 ng / ml). Le-Roy reported a deficiency of 66% in 60 preschoolers (25). There is no data on the VD situation among the child population of the rest of the country.

## STUDIES RELATING VD DEFICIENCY AND ASTHMA

From 2009 onwards, there are many publications that review the impact that VD deficiency would have on a higher prevalence of asthma, worse disease control, higher risk of hospitalization, lower lung function and higher requirements for inhaled corticosteroids. In turn, it is reported that VD3 supplementation for usual asthma treatment would reduce exacerbations (26).

Somashekar (27) in a prevalence study of 88 children between 5-13 years old, 44 asthmatics and 44 healthy matched by age and sex, showed that the average levels of VD in asthmatics were lower, compared to healthy children (12, 88 +/- 1.79 versus 16.49 +/- 1.13, p = 0.02), that the sun exposure time in asthmatics was shorter than in healthy children (p = 0.00) and that the presence of deficiency (<15 ng / ml) was 68.2% in asthmatics and 16% in those controlled. Asthmatics with VD deficiency had worse lung function than asthmatics without VD deficiencies.

Recently, Han (28), in a cross-sectional study, found that asthmatics with low levels of VD exposed to polycyclic aromatic hydrocarbons (PAH), the presence of PAH metabolites was associated with lower lung function, which did not occur in the group of asthmatics with normal levels of VD.

The question remains whether VD deficiency influences asthma control. Kaaviyaa (29) investigated 50 asthmatic children, with persistent moderate asthma or preventive treatment for more than 2 months, measured VD levels and categorized the degree of asthma control according to GINA. 93% of children with poor or partial control of their asthma had VD deficiency, compared with 18% deficiency in a well-controlled group. Havan (30) studied 72 asthmatic children with persistent symptoms, finding lower levels of VD in the asthmatic group, compared to the controlled group (p = 0.004) and in uncontrolled asthmatics observed a higher rate of VD deficiency (<15 ng / ml) and lower rate of normal VD levels (> 20 ng / ml), compared to well-controlled asthmatics (p = 0.007). However, Kavitha (31), found no correlation between VD levels and degree of asthma control among 105 asthmatic children.

Another interesting aspect to evaluate is whether VD supplements reduce asthmatic exacerbations. In this regard, Cochrane Database of Systematic Reviews of double-blind, randomized, placebo-controlled trials (32) evaluated the effect of providing VD in adults (n = 658) and children (n = 435) with mild and moderate asthma, concluding that the contribution of VD reduced the risk of an asthma attack with the need for systemic corticosteroids (SC) from 0.44 attacks / person / year to 0.28 attacks / person / year (RR 0.63, 95% CI: 0.45-0.88) and reduced the risk of asthma attacks in need of emergency attention, hospitalization or both, approximately from 6% to 3% (OR 0.39; 95% CI 0.19-0.78). No effect on lung function or degree of asthma control was demonstrated. Jolliffe, in another systematic review and meta-analysis (33) selected 7 studies with 955 participants (290 under 16 and 665 over 15). The administration of VD2 or VD3 was in bolus (100,000 IU every 2 months), or in a mixed format (bolus 100,000 IU + 400-4,000 IU once a day), for 15 weeks to 1 year. The primary objective of the investigation was "asthmatic exacerbations with the use of SC". It concluded a reduction in asthmatic exacerbations with need of SC from 0.43 events / person / year to 0.3 events / person / year (p = 0.03); in subgroup analysis, that rate reduction was only observed in subgroups with lower previous levels of VD (<10 ng / ml), but not in patients with levels> 10 ng / ml. It should be noted that, in this same study, in the group of <16 years, the changes did not reach statistical significance.

It is also of great interest to observe the relationship between levels of VD in pregnant mothers, a possible VD supplement and the future risk of asthma for the unborn baby. Parr investigated a cohort of Norwegian mothers (34) (n = 61,676) and their children at the age of 7. He conducted a nutritional survey for Vitamin A and VD at 20 weeks of gestation. The highest quintile of VD intake had a lower risk of asthma in their children (3.9%), compared to the lowest quintile (4.4%) (RR = 0.81; 95%

CI = 0.67- 0.97). These results were independent of the intake of VD in the infant at 6 months and the study did not consider sun exposure. Devereaux, in the "Seaton" cohort study (35) studied 2,000 pregnant women, applied a nutrition questionnaire for nutrient intake during the last 3 months ("Scottish Collaborative Group Questionnaire") at 32 weeks of gestation, along with clinical evaluation and data from the clinical record and followed up with the children at 1,2,5,10 and 15 years. A lower intake of VD in mothers was associated with a higher risk of wheezing or asthma at all those ages, except at 15 years of age, at which age they failed to demonstrate such an association.

The question then arises as to whether a prenatal VD supplement could reduce the risk of developing asthma in the child to be born. Shen tried to answer that question through a systematic review and meta-analysis (36). He selected 3 randomized, controlled studies and 33 cohort studies. In the first case, the VD supplement in pregnancy had no effect on the prevalence of wheezing or asthma in children at 3 years of age. In the second type of studies, pooled data from the cohort suggest that the contribution of prenatal VD could reduce the risk of having asthma in children at 5 years in age. Wolsk, in a meta-analysis that included 2 studies (37), concludes that there is a significant effect of an increased intake of VD in the pregnant mother in reducing the risk of asthma in children at 3 years in age, which becomes more evident with higher levels of VD intake prior to pregnancy. Finally, a very recent systematic review and meta-analysis by Shi (38), which included 14 reports of observational studies with 2073 cases of asthma and 1875 cases of wheezing, between 23,030 mother-child binomials, concludes that VD supplement intake during pregnancy reduces the risk of wheezing in the infant (combined OR 0.65; 95% CI: 0.54-0.79) and reduces the risk of asthma (combined OR 0.78; 95% CI: 0, 69-0.89).

## CONCLUSIONS

In this review it becomes clear that in the mother-child population there is a high prevalence of VD deficiency. Patients with a diagnosis of asthma have lower levels of VD and less sun exposure than non-asthmatic patients. Within the group of asthmatic children, lower levels of VD could be associated with lower lung function and lower degree of disease control, although the available data are inconclusive.

The contribution of VD in asthmatic patients could reduce the risk of asthmatic exacerbations and the intake of VD supplements during pregnancy, especially if they have previous high levels of VD, possibly reducing the risk of recurrent wheezing and asthma in unborn children.

Although not all research is consistent with each other and there are still many unanswered questions, with the current evidence it seems reasonable to prevent pregnant mothers from experiencing VD deficiency and VD deficiency should also be prevented in the treatment of children with recurrent wheezing or asthma, monitoring their levels and providing the necessary supplements, especially in those with poor control of their disease.

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