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VITAMIN D AND ASTHMA MANAGEMENT. DOES LOW SERUM LEVELS OF VITAMIN D INFLUENCE ASTHMA CONTROL AND EXACERBATION? – SYSTEMATIC REVIEW

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ABSTRACT

Asthma is a disease characterized by chronic inflammation of the respiratory tract. It is defined by the occurrence of symptoms such as wheezing, shortness of breath, chest tightness, and cough. Restriction of airflow is caused by the contraction of smooth muscles and swelling of the bronchial mucosa, formation of mucus plugs and remodeling of the bronchial wall.

Vitamin D (cholecalciferol) is a steroid hormone that must be supplied to the body. It may be provided with food (ergocalciferol) or synthesized in the skin by solar radiation. Vitamin D produced in the skin has no biological activity, it undergoes hydroxylation in the liver and kidneys to active form – 1,25-dihydroxycholecalciferol.

Aims: The aim of this review is to assess the impact of vitamin D supplementation on asthma management and exacerbation occurrence and severity.

Methods: We conducted this literature review by selecting articles, meta-analyses and reviews from recent clinical trials from Pubmed.

Results: Studies have shown the strong immunomodulatory impact of vitamin D and that there are beneficial effects of vitamin D supplementation in individuals with asthma whose vitamin D levels are insufficient.

Conclusions: Children and adults have provided significant evidence demonstrating the beneficial effects of

vitamin D supplementation in people with asthma, whose vitamin D levels are insufficient. The role of vitamin D status in patients with asthma with adequate vitamin D levels is still a matter of debate. Medical doctors need to monitor the level of vitamin D in their patients and, if necessary, supplement its deficiencies.

Keywords: asthma, asthma exacerbation, vitamin D, vitamin D insufficiency

INTRODUCTION

1. PATHOLOGICAL MECHANISM OF ASTHMA

Asthma is one of the most common respiratory diseases in the world among children and adults. It has various phenotypes and many mechanisms that underlie its pathogenesis. It is a heterogeneous disease characterized by chronic inflammation of the airways which leads to bronchial obstruction and over time – bronchial remodeling. The most important underlying cause of pathological processes in asthma is a reaction mediated by aberrant T helper type 2 lymphocytes (Th2). We can distinguish two types of asthma, depending on the number of lymphocytes present – Th2- high (which is characterized by eosinophilic inflammation) and Th2-low (which is characterized by a higher occurrence of neutrophils). The main mediators in Th2-high type are cytokines (mainly interleukins IL-5, IL-4, IL-13). This type of asthma accounts for approximately 50% of cases in the moderate form and a large proportion of the severe form. The second mechanism of asthma development is Th2-low asthma, in which the role of the mediators can be played by non-Th2 cytokines for example IL-17 and tumor necrosis factor alfa. Also bronchial epithelial cell-derived alarmins (e.g., TSLP, IL-33, and IL-25) are upstream cytokines that initiate immunologic events culminating in airway remodeling [3].New studies show that more compounds may be involved in the inflammatory process in asthma such as protein kinases, adapter proteins, microRNAs, ORMDL3, and gasdermin B. [13]

One of the most important roles in the pathogenesis of asthma is played by the hyperresponsiveness of airway smooth muscle (ASM) cells in response to a stimulus (e.g. allergen, environmental factors). ASM cells are responsible for the bronchoconstriction that we can observe in asthma, but they are also releasing mediators to activate and recruit leukocytes and immune cells to the airways causing inflammation. This mechanism is responsible not only for bronchoconstriction and inflammation but – over time - also for mucus hypersecretion and bronchial remodeling. Some explanations of bronchial hyperresponsive reaction are due to increased histamine from mast cells or increase airway smooth muscle mass. Also, there is an increased vagal tone and increased intracellular free calcium that further enhances airway smooth muscle cell contractility [9].

Nowadays, we also know that the development of asthma depends on the genetic component. Mentioned above gasdermin B and ORMDL3 take part in epithelial cell apoptosis. ORMDL3 is the member of a class of genes that encode transmembrane proteins anchored in the endoplasmic reticulum (ER) and regulate sphingolipid synthesis while GSDMB gene encodes a member of the gasdermin-domain containing protein family [28]. Markers near the ORMDL3/GSDMB genes on chromosome 17q21were first linked to childhood-onset asthma by Moffat et al. (2007) in genome-wide association studies (GWAS) [27]. A polymorphism in a gene locus at position 5q31, which contains the IL4, IL13, and RAD50 genes, has been associated with asthma and atopy in multiple studies, and this locus is also hypomethylated in peripheral blood mononuclear cells (PBMCs) and contains enhancer histone modifications (H3K4me2) in the memory Th2 cells of asthma patients [21].

Asthma exacerbation is defined as a progressive increase in asthma symptoms such as shortness of breath, cough, wheezing, chest tightness, and a progressive decrease in ventilation parameters (PEF, FEV1) requiring a change in treatment [29]. It can be caused by different triggers, for example, allergens, pollution, cold air, and microbes – these agents induce enhanced inflammation in the lungs [15]. Among these triggers, respiratory viruses, especially respiratory syncytial virus (RSV) and rhinovirus (RV) are the major drivers of asthma exacerbations in children and adults [19]. Severe asthma exacerbation is the most dangerous clinical manifestation of asthma.

There are two phases of an asthma exacerbation, which include the early phase and the late phase. The early phase is initiated by IgE antibodies that are sensitized and released by plasma cells. These antibodies respond to triggers in the environment (triggers listed below). The next step is IgE antibodies binding to mast cells and basophils. When an asthma exacerbation trigger is inhaled, the mast cells release cytokines and de-granulate. Released cytokines are histamine, prostaglandins, and leukotrienes. These substances contract the smooth muscle and cause airway tightening. Th2 lymphocytes produce a series of interleukins (IL-4, IL-5, IL-13) and GM-CSF, which communicate with other cells and play a role in further inflammation development. IL-3 and IL-5 help eosinophils and basophils survive and IL-13 is involved in remodeling, fibrosis, and hyperplasia. Then, after a few hours, the late phase occurs, in which eosinophils, basophils, neutrophils, mast cells, and T-cells localize to the lungs, which perform bronchoconstriction and cause inflammation [32].

Table 1. Asthma exacerbation triggers [6].

Asthma exacerbation triggers
• Viral respiratory infections • Bacterial respiratory infections • Allergen exposure • Tobacco smoke • Air pollution (Particulate matter, ozone, nitrogen dioxide, sulfur dioxide, and diesel exhaust) • Obesity • Psychological stress • Poor asthma medication adherence

2. VITAMIN D

Vitamin D is obtained from dietary sources such as oily fish and egg yolks, or photochemical and thermal transformation of the cholesterol precursor 7-dehydrocholesterol in skin exposed to ultraviolet B radiation [17]. It is a steroid hormone that exerts a crucial role in the maintenance of bone and calcium homeostasis. Vitamin D exists in two forms: Vitamin D3, which is the most important source in animals and is produced in the skin; and Vitamin D2 which differs from D3 for a methyl group in C24 and a double bond in C22–C23 and is produced by plants [18].

Vitamin D3 is produced in the skin from 7-dehydrocholesterol by UV irradiation to form pre-D3. Pre-D3 isomerizes to D3 but with continued UV irradiation to tachysterol and lumisterol. D3 is preferentially removed from the skin, bound to DBP (vitamin D binding protein). The liver and other tissues metabolize vitamin D, whether from the skin or oral ingestion, to 25OHD, the principal circulating form of vitamin D. 25OHD is then further metabolized to 1,25(OH)2D principally in the kidney, by the enzyme CYP27B1, although other tissues including various epithelial cells, cells of the immune system, and the parathyroid gland contain this enzyme. 1,25(OH)2D is the principal hormonal form of vitamin D, responsible for most of its biological actions [2]. Vitamin D is known for its calcium absorption and bone modeling function but also has an immunomodulatory effect on innate immunity and adaptive immunity within the body, which explains its links to inflammation-induced epithelial changes in asthma [30,24]. Several studies have associated low vitamin D with asthma flare-ups, poor lung functions, and ineffectiveness of asthma medications [24,34].

Table 2. Main roles of Vitamin D [8].

Main roles of Vitamin D
• Intestinal calcium absorption • Paracellular calcium transport • Renal calcium reabsorption • Renal phosphate reabsorption • Bone metabolism and calcium homeostasis • Immune system regulator

3. VITAMIN D – INFLUENCE ON THE IMMUNE SYSTEM

Vitamin D has an immunomodulatory effect on innate and adaptive immunity within the body and that partially explains its links to inflammation-induced epithelial changes seen in asthma. As a steroid hormone, vitamin D affects cells by binding to the cytoplasmatic vitamin D receptor (VDR). This form of vitamin D bonded to the receptor can then be transferred to the cell nucleus, where it directly affects gene expression. This reaction has been shown to have an immunomodulatory effect on host immune cells, mainly monocytes, dendritic cells, macrophages, but also B and T lymphocytes, as well as on structural cells in the airways [14]. What is more, several studies have assessed the potential relationship between VDR gene

polymorphism and susceptibility to asthma. Makaoui et al. (2020) in their meta-analysis which included 17 studies concerning to VDR gene polymorphisms and asthma risk, found out that there is a statistical significant association between FokI SNP (dominant model and allelic model) and TaqI SNP (homozygote contract model) with asthma risk [25]. Another important mechanism of vitamin D action is epigenetics. Despite the homogenous genome of all cells, they can differentiate by their expression regulation controlled by the proper pattern of methylation. Vitamin D plays an important role in developing the epigenome of hematopoietic stem cells (HSC), which differentiate into over 100 cell types including immune cells. As vitamin D affects mostly innate immunity, it is not surprising, that it also has the most significant impact on the differentiation of monocytes and granulocytes. Moreover, epigenetic modification enables adaptation to variable environmental and internal factors. Stress is a reaction that allows organisms to manage challenges or threats and inflammation is only one of its mechanisms. However, monocytes may transform in many derived cells, for example, macrophages, dendritic cells, or osteoclasts, and in this way mediate other stress reactions. These epigenetic modifications are also under the control of vitamin D signaling pathways [5]. Appropriate function of the immune system is undoubtedly important in developing immunocompetence, which can be defined as the ability to recognize antigen and react adequately to it. This enables not only managing infections or non-communicable inflammatory diseases but also preventing autoimmunity. Immune cell activity relies on the regulation of clusters of HLA, CXCL, and S100A gene families of which many are vitamin D target genes [16].

Table 3. Immunomodulatory effect of vitamin D on inflammatory cells in allergic asthma [14]

Immunomodulatory effect of vitamin D on inflammatory cells in allergic asthma
• Alleviating inflammation in allergic asthma by binding with VDR receptor • Reducing proliferation in ASM cells • Reducing production of pro-inflammatory cytokines in ASM cells • Reducing mucous secretion • Decreasing costimulatory molecules, CCR-7 expression, maturation and antigen presentation in dendritic cells • Changing the balance from Th17 cells to Treg cells evidenced by decrease production of IL-17 and increased production of IL-10 • Inhibiting differentiation and proliferation of B-cells to plasma cells what is believed to play a role in decreasing antibody production • Inhibiting differentiation, maturation, homing and cytokine secretion from mast cells, neutrophils and eosinophils.

METHODS

We conducted this literature review by selecting articles, meta-analyses and reviews from recent clinical trials from Pubmed to investigate if levels of vitamin D have an influence on asthma management and exacerbation. Studies show that asthmatics patients have low levels of vitamin D during an asthma exacerbation, but supplementing it may not reduce the risk of occurrence of exacerbation.

RESULTS AND DISCUSSION

Vitamin D and Asthma Management

CHILDREN

Mansur et al. (2022) in a systematic review provide an overview of the effects of the Vitamin D and supplementation on different aspects before, during pregnancy and newborns. They found that for the non-classical actions of vitamin D, values greater than 40 ng/mL were shown to prevent infectious diseases, predominantly respiratory (such as development of asthma and bronchiolitis), and effects on autoimmune diseases, with which the intervention would favor prevention [26].

In a review from 2022, Salmanpour et al. explored the role of vitamin D in asthma pathogenesis and prognosis, and its effectiveness in treating patients with vitamin D supplements. The result of their review has shown that adding vitamin D3 supplementation to inhaled corticosteroids as an asthma treatment had no significant effect on the time to develop severe asthma and on asthma morbidity. The effect of prenatal vitamin D (cholecalciferol) supplementation on preventing asthma or recurrent wheezing through 3 years of age yet the statistical difference was not significant [31].

Forno et al. (2020) in a randomized clinical trial have studied the effect of vitamin D3 supplementation on severe asthma exacerbations in children with asthma and low vitamin D levels. They included 192 children who were randomized to two groups: vitamin D3, 4000 IU/d or placebo for 48 weeks and maintained with fluticasone propionate, 176 µg/d (6-11 years old), or 220 µg/d (12-16 years old). They found that among children with persistent asthma and low vitamin D levels, vitamin D3 supplementation, compared with placebo, did not significantly improve the time to a severe asthma exacerbation [12].

Sobczak et al. (2023) in metanalysis which included fifteen randomized clinical trials, analyzed the relationship between vitamin D and asthma from the gestational to adulthood period. In their research, they found that supplementation by women during the pregnancy period decreased the wheezing occurrence in their children by 23%, but had no effect on given asthma parameters during the infantile period. This meta-analysis showed varying results depending on the patient's life period [33].

Ducharme et al. (2019) conducted a 7-month, triple-blind, randomized, placebo-controlled, pilot trial of children aged 1–5 years with viral-induced asthma. Participants were divided into two groups to receive two oral doses of 100,000 IU vitamin D3 (intervention) or identical placebo (control) 3.5 months apart, once in the fall and once in the winter. Serum 25-hydroxyvitamin D (25OHD) was measured at 10 days, 3.5 months, 3.5 months + 10 days, and 7 months. The main outcome was that two oral boluses of 100,000 IU vitamin D3 significantly raised overall serum vitamin D metabolites. They found no significant decrease in the rate of asthma flair-ups in the treatment group of 24 children [10].

Luo et al. (2015) meta-analysis included seven enrolled clinical trials that were conducted separately in different countries - Germany, Poland, Turkey, Hershey, India, The Netherlands, and The United Kingdom. Three studies were conducted in children, while 4 studies were in adults. Patients with clinically stable asthma, persistent asthma, and IgE-dependent asthma were, respectively, enrolled in 1 study, while the other 4 studies did not report the clinical features of the enrolled patients. They investigated the effect of giving vitamin D along with asthma controllers and they found that vitamin D supplementation in addition to asthma controllers cannot decrease asthma exacerbation nor improve lung function and asthma symptoms [23].

ADULTS

In the 2023 Cochrane Database systematic review from updated studies and clinical trials, Williamson et al. [36] found that there is no evidence to support a role for vitamin D supplementation or its hydroxylated metabolites in reducing the risk of asthma exacerbations or improving asthma control. Participants with severe asthma and those with baseline 25(OH)D concentrations < 25 nmol/L were poorly represented, so further research investigating this topic is needed.

On the other hand, Wang et al. in 2022 meta-analysis and systematic review were investigating the efficacy of vitamin D in the treatment of COPD and asthma according to the latest updates. 19 randomized controlled studies consisting of 2025 asthmatic patients were included. In the asthma subgroup, FEV1 (forced expiratory volume in one second) was not changed significantly, while FEV1/FVC (forced vital capacity) was improved in the VD (vitamin D) group. ACT (Asthma Control Test) scores for asthma were not significantly changed. For inflammation indicators, IL-6 and IL-10 were statistically equivalent between the VD and placebo groups, while IgE, IL-5, and IL-10 (baseline VD deficiency subgroup) were improved in the VD group. The exacerbation, length of hospital stays, and mortality were statistically equivalent between the two groups. This meta-analysis showed that vitamin D supplementation improved the indicators of asthma, especially in pulmonary function, SGRQ (St George's Respiratory Questionnaire) scores, IL-5, and IgE [35].

Another meta-analysis was conducted in 2019 by Liu et al. Researchers collected data from the largest databases such as OVID, MEDLINE, Web of Science, and PubMed. This study found that asthma patients with low vitamin D levels had lower FEV1 than those with sufficient vitamin D levels. A positive relation was found between vitamin D and FEV1, FVC, ACT. This meta-analysis suggested that serum vitamin D levels may be positively correlated with lung function in asthma patients in both children and adult groups [22].

The next meta-analysis was published in 2024. In it, El Abd et al. studied the effect of vitamin D supplementation on changes in levels of inflammatory biomarkers in patients with asthma. They conducted a systematic review of randomized controlled trials (RCTs) published until November 2022 in six electronic databases evaluating the impact of vitamin D supplementation in any dose, form, administration route, frequency, or duration, compared to placebo in children or adults. Data outcomes included markers like serum IgE and blood eosinophils and type 2 inflammation markers (e.g., sputum eosinophils, fractional exhaled nitric oxide, etc.), anti-inflammatory biomarkers (e.g., interleukin (IL)-10, etc.), markers of non-type 2 inflammation (e.g., high-sensitivity C-reactive protein, etc.), and non-specific biomarkers (e.g., macrophages, etc.). Data were aggregated using fixed or random effect models. The authors observed that vitamin D supplementation in patients with asthma was not associated with lower inflammatory biomarkers related to type 2 inflammation. However, it was associated with higher serum IL-10 compared to placebo [11].

In a randomized controlled trial by Camargo et al. (2021) which included 5250 people, were checking the effect of monthly vitamin D supplementation on preventing exacerbations of asthma or chronic obstructive pulmonary disease (COPD) in older adults. Based on this study, the author concluded that although monthly high-dose vitamin D supplementation had no overall impact on exacerbations of asthma or COPD in older adults, they found evidence of probable benefit among those with severe vitamin D deficiency (baseline 25OHD < 25 nmol/L). These subgroup findings are very similar to results from other vitamin D trials in the literature, particularly those focused on the prevention of COPD exacerbations [4].

Jaura et al. performed a meta-analysis on Cochrane systematic reviews of randomized controlled trials and found that supplementing vitamin D reduces asthma exacerbations [20]. The study observed that administering vitamin D to adult patients with mild-to-moderate asthma reduced the rate of exacerbations by 30% in vitamin D-deficient adults (25(OH)D < 25nmol/L. However, they found no significant reduction in exacerbations for participants with higher baseline vitamin D levels. This study showed that supplementing vitamin D is effective in reducing asthma exacerbations in vitamin D-deficient asthmatic adults.

Chen et al. in their meta-analysis (2021) looked for an association between vitamin D supplementation and improvement of the clinical efficacy of corticosteroids in patients with asthma, measured by exacerbations, ACT score, and lung function to maintain asthma control. They found that Vitamin D supplementation safely reduced the rate of asthma exacerbation but did not improve ACT score or lung function among patients with asthma treated with corticosteroids [7].

CONCLUSIONS

Over the last few years, there have been many discussions about the effectiveness of vitamin D supplementation in patients with asthma. Studies that have been conducted both in laboratory conditions and on living organisms have demonstrated the strong immunomodulatory impact of vitamin D. Both children and adults have provided significant evidence demonstrating the beneficial effects of vitamin D supplementation in people with asthma, whose vitamin D levels are insufficient. The role of vitamin D status in patients with asthma with adequate vitamin D levels is still a matter of debate - more research is needed to determine this relationship. Nevertheless, medical doctors need to monitor the level of vitamin D in their patients and, if necessary, supplement its deficiencies. There is a need for high-quality clinical trials with adequate sample sizes in the coming years. Optimal vitamin D levels for different age groups, genders, ethnicities, and asthma phenotypes should also be considered. Further researches will provide more detailed information on whether vitamin D supplementation should be abandoned as one of the ineffective treatments for asthma, or whether it should be used as one therapy option in combination with other available therapeutic options.

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