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Therapeutic Potential of Vitamin D in Asthma Control

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ABSTRACT

Background: In 2019, according to WHO estimates, 262 million people were affected by asthma, resulting in 455,000 deaths [1]. Asthma, is a chronic inflammatory disease of the airways that causes reversible bronchoconstriction, making it difficult for patients to breathe. Exacerbations of the disease can be caused by a variety of factors but share similar symptoms such as wheezing, coughing, shortness of breath and chest tightness. Severe asthma exacerbations are defined as symptoms that do not respond to inhaled medications and improve only after oral or intravenous steroid administration. Asthma-related deaths often occur during exacerbations. Vitamin D, which is produced naturally in the body and found in some foods, is a steroid-derived vitamin. Adequate doses of this vitamin, administered through medication or supplements, can be used to maintain its proper levels in the organism. Vitamin D is essential for regulating calcium levels in the body and for bone remodeling. It also has immunomodulatory effects, affecting both innate and adaptive immunity. This partly

explains its association with changes in the airway epithelium that occur as a result of inflammation in asthma.

Aim of the study: The study aims to summarize the current knowledge on the relationship of vitamin D with asthma symptom control.

Material and methods: The present study is based on literature available in scientific databases from 2013-2016, such as PubMed, Corchane Library and Google Scholar, using the following keywords: "vitamin D" and "asthma."

Results and conclusions: Vitamin D deficiency is prevalent in children and adults worldwide. A critical analysis of the literature reveals that the therapeutic administration of vitamin D has no apparent advantage in treating asthma, especially in children. Nevertheless, for adults with mild asthma, vitamin D supplementation shows promise for improved outcomes. However, there is a pressing need for large-scale clinical trials to determine the efficacy and safety of this therapeutic approach for both age groups.

Key words: „asthma”; „vitamin D”; „vit D”

The description and epidemiology of asthma:

Asthma is a disease that is characterized by airway inflammation, airway hyperresponsiveness, and airflow limitation. These symptoms can lead to respiratory issues such as coughing, wheezing, and shortness of breath [2]. Asthma in most cases has an atopic basis, representing a multifactorial and multigene disorder. This phenomenon implies the presence of different phenotypes, i.e. groups characterized by common combinations of characteristics, including clinical presentation, demographics, among others [3]. The pathogenesis of this disease is diverse, allowing for identification of subgroups based on causative factors such as genetics, environment, and immunology [4]. The most severe clinical form of asthma is the asthmatic state, which is characterized by periodic exacerbations of the disease that pose an immediate threat to life. Patients with persistent attacks require hospitalization, often administration of oxygen and even mechanical ventilation [3]. The primary objective of asthma treatment is to

achieve symptom control, which reduces the risk of future exacerbations and progressive loss of lung function. This is particularly challenging for patients with difficult asthma [2].

It is estimated that approximately 300 million people worldwide are affected, and this number is expected to increase by approximately 30% in the next few years. The prevalence of the disease varies widely between countries. In 2017, asthma as a disease had the highest prevalence and mortality rates in the Oceania region. At the same time, the lowest prevalence rate was in South Asia, while the lowest mortality rate was in the Eastern Europe region. According to the Global Burden of Disease estimates prepared by the Institute for Health Metrics and Evaluation, 4.9% of the population in Poland suffered from asthma in 2017. Gender was also affected, as women were more likely to be diagnosed with the disease [3].

The description of the metabolism vitamin D

The skin synthesizes most of the vitamin D in humans through the conversion of 7-dehydrocholesterol into cholecalciferol (vitamin D₃) under the influence of ultraviolet solar radiation. Additionally, there is a bioactive form of plant-derived vitamin D, known as ergocalciferol (vitamin D₂) [5]. It is now commonly used for food fortification and as a dietary supplement. Structurally, vitamin D₂ and vitamin D₃ are similar. However, vitamin D₂ contains one extra methyl group on carbon 24 and a supplementary double bond between carbons 22 and 23. Despite these differences, they are considered equivalent in terms of metabolic activation [6]. The amount of dietary vitamin D is minimal in comparison to the overall vitamin D present within human organisms and is affected by an individual's specific diet [7].

In general, food sources of vitamin D are limited and include oily fish, cod liver oil, and egg yolks, etc. It's crucial to have a balanced dietary intake if sunshine exposure is inadequate. In northern regions, people rely on dietary sources to maintain sufficient vitamin D levels, especially during the winter months [5], [7].

It's important to note that vitamin D is not biologically active until converted into its active form. To accomplish this, vitamin D enters the bloodstream through, either the skin or diet and is carried by the vitamin D binding protein (DBP) to the liver [8]. In the liver, the enzyme vitamin D 25-hydroxylase, comprising of hydroxylases that fall under cytochrome P450 (CYP27A1, CYP3A4, and CYP2R1), metabolizes vitamin D to 25-hydroxyvitamin D (25(OH)D) [9]. This is the predominant circulating form of vitamin D [8]. However, despite this, it is virtually biologically inactive. 25(OH)D is transported through DBP to the kidneys,

where it undergoes further hydroxylation in the mitochondria via the enzyme 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) [9] , [10] . This biochemical pathway generates 1,25(OH)₂D, also referred to as calcitriol, which represents the active form of vitamin D. Once synthesized, 1,25(OH)₂D interacts with the specific nuclear VDR to induce its function [10].

Previous research suggested that the kidney was the sole source of calcitriol production; however, current knowledge indicates that CYP27B1 expression is widespread in other tissues, leading to the formation of calcitriol from calcidiol in various organs aside from the kidneys. Skeletal and cardiac muscles, T and B lymphocytes, macrophages, liver, brain, placenta, breast, colon, prostate, and bronchi are all included in this list [11]. The activity of 1 α -hydroxylase (CYP27B1) is influenced by a variety of factors, including calcium concentration, parathormone (PTH), fibroblast growth factor 23 (FGF-23), and Klotho. Furthermore, it is negatively affected in a feedback loop by 1 α ,25(OH)₂D [8] . It should be noted that vitamin D can be considered a hormone, since vitamins are substances that cannot be synthesized in sufficient quantities by the body and must be obtained from the diet.

Table No.1 shows the established ranges for serum 25-hydroxyvitamin D concentrations based on discussions among experts in the field.

Vitamin D level	Concentration
Deficiency	< 20 ng/mL (< 50 nmol/L)
Suboptimal	20-30 ng/mL (50-75 nmol/L)
Optimal	30-50 ng/mL (75-125 nmol/L)

These ranges were determined through post-conference networking and are widely accepted in the scientific community. General practical guidelines for vitamin D prophylaxis were developed, providing updated recommendations for Central European neonates, infants, children, adolescents, adults, pregnant, breastfeeding women and the elderly [12].

Theoretical link between vitamin D and asthma:

Circulation of 25(OH)D is increased by administration of vitamin D3, vitamin D2, or 25(OH)D, which acts as a substrate for acts as a substrate for CYP27B1 expressed not only in the kidney but also in multiple other tissues [13] . Inflammation and infection induce CYP27B1 expression in the airway and leukocytes, making it relevant for asthma [14].

The active vitamin D metabolite 1,25(OH)2D is synthesized in the lung as a result [15] . 1,25(OH)2D binds to the vitamin D receptor (VDR) to stimulate antimicrobial activity (such as by increasing antimicrobial peptide expression) and exhibit anti-inflammatory effects (such as by inducing the anti-inflammatory cytokine interleukin 10 (IL-10), reducing pro-inflammatory tumor necrosis factor (TNF) and inducible interferon gamma (IFN- γ -inducible) chemokines, and inhibiting stimulated lipopolysaccharide (LPS-stimulated) production of reactive oxygen species). This combination of activities with antimicrobial, antiviral, and anti-inflammatory effects could potentially lower the risk of exacerbations. These exacerbations are frequently triggered by respiratory infections, leading to unregulated pulmonary inflammation [13][15].

1,25(OH)2D has been demonstrated to increase the responsiveness to inhaled corticosteroids (ICS) in the production of IL-10, which is of particular significance for asthma. This finding suggests that administering vitamin D or 25(OH)D may help reduce the risk of asthma exacerbation and improve symptom control when used in combination with ICS, as well as independently [13] . There is ongoing debate regarding the optimal serum 25(OH)D concentration due to individual variability. This may have potential implications for reducing the risk of asthma exacerbations.

Review

Effect of vitamin D supplementation on asthma exacerbation in children and adolescents.

Forno et al. [16] conducted a randomized controlled trial with 192 participants, including 77 females and 115 males, with an average age of 9.8 years. This intervention lasted for 48 weeks. The participants were randomly assigned to either the intervention group, who received 4000 IU of vitamin D supplementation and fluticasone propionate maintenance, or the control group, who received a placebo and fluticasone propionate maintenance. The study found no significant difference in the time to severe asthma exacerbation between the two

groups, and the utilization of inhaled corticosteroids remained steady throughout the investigation.

Bruno et al. [17] conducted a review of eight randomized controlled trials (RCTs), including one with a parallel design and another with a crossover design, that involved 573 children aged 3 to 18 years. One moderate-quality study reported a statistically significant reduction in emergency department (ED) visits for children given vitamin D treatment. Other studies did not investigate the primary outcomes of ED visits and hospitalizations. Children who received vitamin D had a reduced risk of asthma exacerbations. However, no significant effects were found on asthma symptom scores or lung function. At the end of the intervention, the serum 25(OH)D level was higher in the vitamin D group.

In Kavitha et al.'s study [18], 105 pediatric participants were classified as having controlled asthma (47.6%), partially controlled asthma (30.5%), or uncontrolled asthma (21.9%). The findings revealed no statistically significant differences in median serum 25(OH)D levels among the three groups concerning asthma control. While the majority of core spirometric parameters exhibited no statistically significant correlation with serum vitamin D levels, two exceptions were observed for Forced Expiratory Flow 25 (FEF25) and Peak Expiratory Flow Rate (PEFR).

On the other hand, Puranik and colleagues [19] performed a meta-analysis of three observational studies that evaluated the association between vitamin D levels and asthma exacerbations in children. Their results indicate that low serum 25-hydroxyvitamin D levels (<30 ng/mL) are common during asthma exacerbations.

Similarly, Niruban et al. [20] found an elevated risk of current and future asthma in individuals with 25(OH)D levels under 50 nmol/L in their study.

Additionally, a review of evidence investigated the correlation between vitamin D levels and respiratory conditions like asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis. The findings suggest that while vitamin D deficiency is common during exacerbations of these illnesses, it is not likely to be the primary cause. The review found that low levels of vitamin D are associated with an increase in asthma exacerbations, although the exact mechanism of this effect is not yet understood [21].

In the meta-analysis [22] found that there were no significant changes in the exacerbation rate among children, as determined by asthma control test scores, exhaled nitric oxide fraction, IL-10 levels, and incidents of adverse events after taking vitamin D supplements, in contrast to the adult population.

Effect of vitamin D supplementation on asthma exacerbation in adults.

Jin et al. [23] conducted a study examining the effects of vitamin D on collagen synthesis in human lung fibroblasts, the cells responsible for collagen production in the airways. They found that both the expression of type I collagen and the activity of enzymes involved in collagen synthesis, such as PRMT11, were reduced by the effects of vitamin D. This led to the conclusion that vitamin D may have anti-inflammatory and anti-fibrotic effects in the airways, which in turn may help reduce the severity of asthma as well as prevent airway remodeling.

Jaura and colleagues [24] conducted a meta-analysis of controlled trials and concluded that adding vitamin D supplements to treatment can reduce asthma exacerbations. Results show a 30% reduction in exacerbation rates among adults with mild-to-moderate asthma who were vitamin D-deficient. The study included 92 participants from three randomized control trials, and the number needed to treat (NNT) was calculated to be 4.3. The randomized controlled trials involved 764 participants, and researchers found that vitamin D supplementation did not significantly reduce exacerbations in participants with higher baseline vitamin D levels. However, in participants with low baseline vitamin D levels, vitamin D supplementation led to a reduced asthma exacerbation rate of 0.19 events per participant-year compared to 0.42 events per participant-year ($P = .046$). The participants in the trials were administered an overall average of 900 IU/day of vitamin D (range, 400-4000 IU/d). This study demonstrates the efficacy of vitamin D supplementation in reducing asthma exacerbations among vitamin D-deficient adults with asthma.

A study by Schrupf et al. in 2020 [25] suggests that TGF- β 1 may impair the action of vitamin D in promoting host defense mechanisms in the airways by interfering with the signaling pathway activated by vitamin D and reducing the expression of key genes involved in host defense. These findings may provide an anchor for the development of new therapies for respiratory diseases, more toward chronic obstructive pulmonary disease (COPD) than asthma, as targeting the interaction between vitamin D and TGF- β 1 may be a promising approach to improve airway host defense.

According to a systematic review by Salameh and colleagues [26], it can be concluded that the adult studies they analyzed provide evidence that vitamin D has beneficial effects on the airways, including inhibition of airway smooth muscle cell contraction and remodeling, reduction of inflammation, and regulation of collagen synthesis.

In contrast, Camargo and colleagues [27] performed a post hoc analysis on data obtained from a placebo-controlled, double-blind trial, where monthly vitamin D supplementation was administered to older adults. Among 775 patients with either asthma or COPD who were enrolled in the study at Auckland, New Zealand. The participants had an average age of 67 years, 56% were male, and were observed for a mean duration of 3 years. Over a period of three years, participants were administered 100,000 IU of vitamin D or placebo every month. Additionally, they received a one-time initial dose of 200,000 IU of vitamin D or placebo. Results indicated that vitamin D supplementation did not have a significant impact in preventing asthma exacerbation.

The second phase of the cohort study by Solidoro et al [28] , which included vitamin D supplementation (100,000 IU IM x1 followed by 5,000 oral doses weekly and 400 IU oral doses daily) for one year, provides additional support for the efficacy of vitamin D supplementation in adult patients. They found that in patients with baseline vitamin D levels <20ng/mL, there was a reduction in asthma exacerbation rate, circulating eosinophils, and need for oral corticosteroid courses and improvement of airway obstruction, in contrast to asthmatic patients with higher initial levels of vitamin D. This research suggests that vitamin D supplementation in asthmatic patients with low levels of vitamin D is beneficial for reducing flare-ups.

Current trends in clinical research on the relationship between asthma and vitamin D:

Analyzing Pubmed database, this discovery is that between 2018 and 2023, approximately 53 clinical trials were conducted that focused on the relationship between vitamin D and asthma control. These studies included analyses of children, adolescents and adults, but the population of pregnant women and their newborns was of particular interest.

Currently, most studies have focused on pregnant women to understand the potential impact of vitamin D supplementation on the risk of asthma in their offspring. However, due to the methodological diversity and limitations of the studies, further analysis is needed before firm conclusions can be drawn.

In summary, the clinical trial included a diverse range of age groups, such as pregnant women, newborns, children, adolescents, and adults. In the context of a more complete understanding of the relationship between vitamin D and asthma, more studies are needed that take into account the diversity of age groups and diverse populations. However, further well-designed studies are needed to define this relationship more precisely.

Conclusion:

The lack of vitamin D is a significant health issue that affects both children and adults worldwide. The thorough examination of the important scientific studies on the effectiveness of vitamin D in treating asthma has resulted in noticeable discoveries.

In regards to treating pediatric asthma, it is important to exercise caution when assuming the therapeutic benefits of vitamin D, as its deficiency is quite common. The literature review indicates that administering vitamin D may not consistently provide clear benefits, highlighting the need for further investigations. The theoretical basis of how vitamin D could influence asthma has been explained, but achieving complete compatibility with clinical practice requires more empirical research.

Regarding adults with mild asthma, the literature review suggests promising factors linked with the benefits obtained from taking vitamin D supplements. The established theoretical basis of vitamin D influence on asthma inspires confidence. Nevertheless, it is crucial to acknowledge the limitations inherent in the analyzed studies. The review is constrained by the age distribution of the patients and the duration of the observational period. In studies with a mixed population, adults constitute the majority of the cohort, potentially biasing outcomes in favor of this age group and labeling the summary as an adult population.

In conclusion, although there is promise regarding the therapeutic potential of vitamin D in controlling asthma, further well-designed clinical studies are essential to determine its comprehensive role. To achieve a comprehensible and well-structured understanding of vitamin D influence on asthma management, it is imperative to conduct studies that incorporate both pediatric and adult cohorts. Such studies should also consider age-specific variations and varying observation durations, resulting in a nuanced comprehension of the topic.

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