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2734 17 Avenue SW,
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+15878858911
editorial-office@sciformat.ca

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THE ROLE OF VITAMIN D IN BRONCHIAL ASTHMA: MECHANISMS, CLINICAL OUTCOMES, AND THERAPEUTIC IMPLICATIONS

Vladyslav Tetarchuk *(Corresponding Author, Email: vladek1708@hotmail.com)*
Wielospecjalistyczny Zespół Opieki Zdrowotnej "Bolesławiec-Zgorzelec", ul. Lubańska 11-12, Zgorzelec, Poland
ORCID ID: 0009-0003-6743-6319

Daria Shchebetun
Zespół Opieki Zdrowotnej, Kościuszki 74, Wągrowiec, Poland
ORCID ID: 0009-0004-0105-2512

Andrei Trutsko
Uniwersyteckie Centrum Kliniczne Warszawskiego Uniwersytetu Medycznego ul. S.Banacha 1A, Warszawa, Poland
ORCID ID: 0009-0003-5674-7971

Olena Abramchuk
Centrum Medyczne Unimed, ul. Młodej Polski 7, Kraków, Poland
ORCID ID: 0009-0000-2604-0287

Artem Shchebetun
Zespół Opieki Zdrowotnej, Kościuszki 74, Wągrowiec, Poland
ORCID ID: 0009-0004-3044-4793

Anastasiia Tanko
Szpitale Pomorskie Sp. z o.o., Szpital św. Wincentego a Paulo, ul. Wójta Radtkego 1, Gdynia, Poland
ORCID ID: 0009-0005-6931-5718

Vlada Tetarchuk
Wielospecjalistyczny Zespół Opieki Zdrowotnej "Bolesławiec-Zgorzelec", ul. Lubańska 11-12, Zgorzelec, Poland
ORCID ID: 0009-0002-7754-4113

ABSTRACT

Background. Bronchial asthma is a heterogeneous chronic inflammatory disease that is frequently not optimally controlled even with modern background therapy. Additional factors affecting inflammatory processes and clinical courses are actively investigated, notably vitamin D status, because vitamin D participates in immune system regulation and airway structural cell function.
Aim. To summarize current knowledge regarding the association between vitamin D status and the clinical course of bronchial asthma in adults, describe potential pathophysiological mechanisms, and critically evaluate the clinical efficacy and safety evidence of vitamin D supplementation.
Materials and Methods. This paper reviews observational studies, randomized controlled trials, systematic reviews, and meta-analyses concerning vitamin D's role in asthma, focusing primarily on adult patients.
Results. Experimental findings indicate vitamin D influences the immune system, airway type 2 inflammation, and airway remodeling. Although several observational studies link low 25(OH)D levels to adverse clinical asthma features, intervention trial results remain inconsistent. A recent Cochrane review found no convincing evidence that vitamin D supplementation reduces severe exacerbations or improves asthma control and lung function.
Conclusions. Although mechanistic rationale suggests a potential role for vitamin D in asthma pathogenesis, current evidence lacks proof of clinical value for supplementation. Therefore, based on current evidence, vitamin D supplementation cannot be recommended as an additional controller therapy for patients with bronchial asthma.

KEYWORDS
Bronchial Asthma, Vitamin D, Asthma Exacerbations, Lung Function, Supplementation

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Introduction

Bronchial asthma is a chronic disease of the airways, characterized by variable respiratory symptoms and variable expiratory airflow limitation, including bronchial hyperresponsiveness, mucosal inflammatory infiltration, and structural airway remodeling [1].

Beyond its classical function in calcium-phosphate metabolism, vitamin D is increasingly investigated for its role in immunoregulation and cellular activity. Its active form, calcitriol, binds to the vitamin D receptor (VDR), which is expressed by various cells, including immune cells and airway structural cells [2]. Although observational studies frequently associate reduced 25(OH)D concentrations with greater asthma severity, impaired respiratory function, and higher exacerbation rates [4], association does not necessarily imply causality. Furthermore, while individual supplementation studies often appear promising, more comprehensive pooled analyses have failed to demonstrate lasting clinical efficacy [6, 7, 8].

The objective of this review is to summarize current data on the association between vitamin D status and clinical outcomes of asthma in adults, consider proposed pathophysiological mechanisms, and critically evaluate the evidence regarding the efficacy and safety of vitamin D supplementation.

Methodology

The primary investigative scope targeted peer-reviewed scientific literature published between 2016 and 2026. This decade-long window ensures that the compiled evidence reflects modern insights into airway type 2 inflammation, high-dose randomized controlled trials (RCTs), updated Cochrane meta-analyses, and contemporary clinical guidelines, including the Global Initiative for Asthma (GINA) 2026 strategy report. However, landmark clinical trials and seminal observational studies from preceding years were also included to maintain comprehensive historical and foundational context.

Information retrieval was systematically executed across major international scientific databases, including PubMed/MEDLINE, Google Scholar, EMBASE, Scopus, and the Cochrane Database of Systematic Reviews. The electronic search strategy incorporated targeted, boolean-linked keyword combinations designed to evaluate the pathophysiological mechanisms, clinical outcomes, and therapeutic efficacy of vitamin D in adult asthma, such as:

- ("vitamin D" OR "cholecalciferol" OR "calcifediol") AND ("bronchial asthma" AND "adults");
- ("25-hydroxyvitamin D" OR "25(OH)D") AND ("FEV1" OR "lung function" OR "airway hyperresponsiveness");
- ("vitamin D supplementation") AND ("asthma exacerbations" OR "systemic corticosteroids");
- "vitamin D receptor" AND ("airway smooth muscle" OR "airway remodeling" OR "TGF-beta");
- ("immunomodulatory effects" OR "type 2 inflammation") AND "vitamin D" AND "asthma".

Retrieved manuscripts were screened and deemed eligible for detailed analysis if they satisfied at least one of the following operational criteria:

- Evaluated the biological mechanisms of active vitamin D or VDR signaling on airway structural cells, smooth muscle contractility, or extracellular matrix deposition;
- Assessed the association between serum 25(OH)D concentrations and clinical parameters of asthma severity, lung function (FEV_1, FVC, FEV1/FVC) or systemic inflammatory biomarkers in adults;
- Investigated the clinical efficacy and safety of oral vitamin D supplementation in reducing severe exacerbations, improving Asthma Control Test (ACT) scores, or enhancing quality of life in prospective RCTs or pooled meta-analyses;
- Critically appraised methodological heterogeneity, dosage schedules (daily low-dose vs. bolus dosing), or differential baseline vitamin D thresholds across major systematic reviews.

Conversely, studies were systematically excluded if they focused exclusively on pediatric populations (<18 years of age) without providing disaggregated, independent subgroup reporting for adult asthmatics. Non-peer-reviewed commentaries, editorials lacking original data, popular nutritional literature, non-English publications without accessible full text, and studies investigating vitamin D exclusively in non-asthmatic chronic obstructive pulmonary disease (COPD) or active pulmonary tuberculosis were also excluded from the final synthesis.

Results

Vitamin D and the Pathophysiology of Bronchial Asthma

Immunoregulatory Role of Vitamin D

One of the key components of the pathogenesis of asthma, particularly in the allergic phenotype, is the type 2 immune response mediated by specific immune cells and their associated cytokines. After allergen exposure in the airways, antigen-presenting cells such as dendritic cells are activated and process the allergen. Upon presentation of antigenic peptides to naive CD4+ T-lymphocytes in the appropriate microenvironment, they can differentiate into Th2 cells. IL-4 stimulates IgE production by B-cells. Upon subsequent contact with the allergen, the antigen-specific IgE bound to the high-affinity receptor FcεRI on mast cells is activated, and releases mediators such as histamine and leukotrienes. These mediators cause bronchoconstriction, mucosal edema and increased mucus secretion. IL-5 is responsible for the development, differentiation and activation of eosinophils which release granular proteins and other mediators that can cause damage to the epithelial barrier and sustain inflammation. Vitamin D has been described to influence the immune system. Experimental studies showed that vitamin D affects the development of T-cells as well

as the function of antigen-presenting cells and the production of specific cytokines. In addition, it affects the balance between effector and regulatory T-cells. However, these experimental results do not provide any evidence for an anti-inflammatory effect of vitamin D in patients with asthma. El Abd and colleagues [5] performed a systematic review and meta-analysis of 68 observational studies and 3 interventional studies. Most analyses did not find any significant correlation between serum 25(OH)D levels and various inflammatory markers in asthma patients. An inverse correlation between serum 25(OH)D and total IgE levels was found in a subgroup of low-risk-of-bias studies. However, the majority of the studies were pediatric and thus cannot be easily extrapolated to adult patients with asthma. Thus, while there is some scientific interest in the potential immunoregulatory effects of vitamin D, its clinical relevance in adult patients with asthma remains to be determined.

- **Vitamin D and Airway Remodeling**

Airway remodeling comprises structural changes in the bronchial wall developing as a result of chronic inflammation and impaired epithelial repair. These changes consist of subepithelial thickening, smooth muscle mass increment, goblet cells count modifications, and extracellular matrix deposition.

TGF-β is involved in the control of fibroblasts and myofibroblasts as well as of the synthesis of collagen, fibronectin and other extracellular matrix proteins. The increase in bronchial smooth muscle mass, by hypertrophy and/or by hyperplasia of smooth muscle cells, as well as an increased production of mucus, contribute to bronchial hyperresponsiveness and persistent airflow limitation.

An experimental study was conducted by Britt et al. to examine the effects of calcitriol in human airway smooth muscle cells obtained from surgical lung tissue samples. The authors demonstrated that the active form of vitamin D can attenuate some of the effects of TNF-α and IL-13, including enhanced cellular calcium responses and collagen/fibronectin deposition [2]. The findings from this study provide further evidence that VDR signaling influences airway structural cells.

A systematic review by Salameh et al. summarized experimental evidence on the potential impact of vitamin D on airway remodeling [3]. Experimental models, such as in vitro studies, however, do not show that oral vitamin D intake protects against bronchial remodeling or improves the lung function of the patients. The clinical significance of these mechanisms remains uncertain.

- **Vitamin D Status and Clinical Outcomes of Asthma**

Serum 25-hydroxyvitamin D [25(OH)D] concentration is measured to assess vitamin D status. In several studies on observational studies, lower levels of 25(OH)D were associated with more severe symptoms, less favorable lung function and more exacerbations. A systematic review, by Abi-Ayad et al., was conducted to examine the association between 25(OH)D and FEV1, FVC and FEV1/FVC in children and adults with asthma [4].

Interpretation of these data is limited by potential confounding. 25(OH)D levels are influenced by age, BMI, diet, physical activity, sun exposure, and co-morbidity, all of which may be associated with asthma severity. The factors listed above can also influence 25(OH)D levels and can be associated with the severity of asthma. Reverse causality is also possible because patients with more severe symptoms of asthma might spend less time out of doors and be less active.

- **Vitamin D Status and Disease Severity**

Observational studies have shown lower levels of 25(OH)D in patients with uncontrolled asthma. However, asthma severity is influenced by many factors, including the patient's inflammatory phenotype, structural alterations of the airways, comorbidities, adherence to therapy and treatment response. Therefore, a low level of 25(OH)D is not an independent marker of severe asthma and does not cause deterioration of the disease.

- **Vitamin D and Lung Function**

Studies that have investigated the association of 25(OH)D with FEV1, FVC and

FEV1/FVC had mixed results. They may vary with age, asthma severity, baseline 25(OH)D and other confounding factors. FEV1 and FVC are two parameters of lung function that measure different aspects of the respiratory system and can change independently of each other. The existing studies do not provide sufficient evidence to determine whether low 25(OH)D concentrations are an independent factor for declining lung function in adult asthmatics [4].

- **Vitamin D and Exacerbation Risk**

In observational studies lower levels of 25(OH)D were associated with an increased risk of asthma exacerbations [6, 14, 15]. Potential mechanisms could be an effect of vitamin D on the immune system or an increased susceptibility to infections. However, the association does not imply that an increase in vitamin D levels by means of supplementation can reduce the risk of asthma exacerbations [8, 14]. Randomized controlled trials are needed to assess causal effects.

- **Vitamin D Supplementation: Clinical Evidence**

The clinical efficacy of vitamin D supplementation has been evaluated in a number of randomized trials as well as in meta-analyses. Results obtained in these studies can vary considerably depending on the age of the patients, their baseline levels of 25(OH)D, the form of vitamin D used, the dosage as well as the endpoints of interest [6, 8, 14, 15].

Randomized Trials in Adults

The VIDA trial, a large trial of 408 adults with symptomatic asthma and low baseline levels of 25(OH)D, did not find that addition of vitamin D3 to standard treatment reduced the rate of treatment failures as opposed to placebo [9]. The ViDiAs study, with 250 adult patients with persistent asthma, was also designed as a double-blind, placebo-controlled study with bolus doses of vitamin D3 over a period of 1 year. However, no significant effect of the intervention on the time to the first severe asthma exacerbation was found [10]. In the ACVID study, 112 adult asthma patients with vitamin D insufficiency were randomized to receive calcifediol or placebo for 6 months. After 6 months the ACT score increased on average by +3.09 points in the calcifediol group compared to +0.57 points in the placebo group. In comparison with the placebo group the increase in ACT score in the calcifediol group was 3.66 points (95% CI: 0.89– 5.43; $p < 0.001$) [11]. These findings, although positive, need to be confirmed in large, independent trials. Calcifediol was used instead of standard cholecalciferol. The study by Watkins et al. included 32 adults with mild-to-moderate asthma. They received 125 µg of vitamin D3 per day for 12 weeks. Twenty-seven participants (84%) completed the study. There was a small, but statistically significant difference in the change of FEV1/FVC ratio between the vitamin D group and the placebo group ($p = 0.040$). However, there was no significant difference in the ACT, FEV1, FVC, and a number of inflammatory markers between the two groups. It is worth noting that the dosage of 125 µg of vitamin D3 was used instead of the more frequently used form cholecalciferol. An erratum published by the publisher of the study clarified the unit of the dosage [13]. It is also worth noting that this study had a very small number of participants and a short follow-up period, therefore its results can only be interpreted as evidence of clinical efficacy with caution.

Meta-Analyses of Randomized Trials

Liu et al. included 10 randomized trials with 1,349 participants in their meta-analysis

[6]. The pooled analysis showed a decreased risk of exacerbations with a RR of 0.69 (95% CI: 0.41–0.88). There was no significant effect on ACT, FEV1, or FeNO in the pooled analysis. The exacerbation finding therefore cannot be interpreted as proven effect in adults. The subgroup outcome for FEV1 with baseline values <70% predicted relied on limited data and therefore has to be interpreted with caution.

The meta-analysis of 15 randomized trials of different age groups by Sobczak and Pawliczak [7] found, for the adult subgroup, a small but statistically significant increase in the ACT score (MD = 1.80; 95% CI: 0.12–3.49; $p = 0.0359$), however, heterogeneity was extremely high ($I^2 = 99\%$). This reduces confidence in the pooled estimate and prevents considering the result as robust evidence of clinical benefit.

Cochrane Systematic Review

An updated Cochrane review by Williamson et al. included 20 randomized trials involving 2,225 individuals (1,070 adults and 1,155 children) [8]. For the primary outcome—the proportion of patients experiencing at least one exacerbation requiring systemic corticosteroids—the pooled estimate showed no risk reduction with vitamin D supplementation (OR = 1.04; 95% CI: 0.81–1.34). No convincing evidence of improved asthma control or lung function was observed. The authors noted that there was underrepresentation of participants with very low levels of 25(OH)D (<25 nmol/L) and with severe asthma. Overall, the review does not support the routine use of vitamin D as an adjunctive therapy for asthma control.

Safety

There was no evidence of an increased incidence of serious adverse events associated with the use of vitamin D in the Cochrane review [8]. Individual studies have reported on hypercalciuria, hypervitaminosis D, nephrolithiasis and other events of varying severity such as gastrointestinal symptoms. Adverse event risk depends on dose, duration, baseline patient status, and coexisting conditions. An optimal vitamin D dosing scheme specifically for asthma management has not been established. Correction of confirmed vitamin D deficiency should follow general clinical indications and safety guidelines. Vitamin D supplementation must not replace ICS-containing controller therapy.

Emerging Synthesis Data from 2026

In May 2026, an overview of systematic reviews and meta-analyses investigating the effects of vitamin D supplementation in patients with asthma was published, comprising

21 reviews [14]. There was some evidence of a beneficial effect of vitamin D supplementation on the risk of asthma exacerbations; however, there was limited and very heterogeneous evidence on other outcomes, including asthma symptoms, lung function and markers of inflammation. A major limitation of the included reviews was the substantial overlap of primary studies between the reviews, i.e. most reviews included the same RCTs. Therefore, the number of reviews does not equal the number of independent confirmations of the effects. These findings are not necessarily in contrast with the findings of the Cochrane review as there are several reasons for differences in estimates, including differences in inclusion criteria, trial composition, age of the patients, and methods for statistical pooling. Thus, evidence from primary RCTs and high quality systematic reviews, particularly those that have analyzed data for adult patients separately, should be used for clinical decision making. While the evidence for a beneficial effect of vitamin D supplementation in patients with asthma is emerging, there is insufficient evidence to support the use of vitamin D supplementation as an adjunctive treatment for all patients with asthma [8, 14].

Implications of Vitamin D Status for Clinical Practice

Vitamin D deficiency can be treated as a separate clinical condition and, as an adjunct to anti-inflammatory asthma therapy, vitamin D supplementation can be used to improve the clinical course of asthma [8, 14]. Vitamin D deficiency as an independent disease has to be diagnosed and treated. In contrast, the use of vitamin D supplementation as an adjunctive treatment to improve the clinical course of asthma has to be proven to have added value compared to the current treatment with other drugs [1, 8]. Serum 25(OH)D can be used as the best measure to assess vitamin D status, although different cut-offs are used to classify individuals as vitamin D deficient or sufficient [14]. Therefore, results from studies using different cut-offs cannot be compared. It is especially important not to generalize results from studies with severely vitamin D deficient patients to individuals with normal vitamin D levels at baseline and vice versa [8, 14]. The assessment of other risk factors and associated diseases, diet, body mass index, physical activity and current medication as well as possible reasons for insufficient sun exposure is necessary [1]. Treat vitamin D deficiency as an independent condition and continue to treat asthma with the appropriate anti-inflammatory treatment. The patient must be informed that correction of vitamin D deficiency is not a substitute for the antiinflammatory treatment of asthma and that he or she must not decrease the dose of the inhaled corticosteroid or other asthma medications on their own. At present, there is no evidence to support routine 25(OH)D measurement in adults with asthma and, therefore, no evidence to recommend vitamin D as an adjunctive treatment for asthma control in this group of patients [1, 8, 14]. Therefore, decisions regarding measurement of vitamin D and treatment with vitamin D should be made on the basis of other clinical indications.

Asthma as a Public Health Issue

Asthma is a chronic disease of individuals but also a public health problem. Symptoms, attacks, restricted physical activity, disturbed sleep and the use of health care services for emergencies are some of the factors that can affect the quality of life, work and health care services of patients with asthma [1]. While there is a public health importance to vitamin D in asthma, the frequency of low serum 25(OH)D concentrations is likely to be highest in more severe asthma patients and this can be explained by other factors such as lifestyle, co-morbidities, obesity, reduced physical activity, poor diet and inadequate exposure to sunlight [4, 8]. From a public health perspective, the use of effective controller therapy is more important than adjunctive nutritional interventions. While certain nutritional interventions may be of use in certain situations, they should not distract from the need to ensure timely diagnosis, correct use of the inhaler,

adherence to treatment and management of other risk factors. In settings with limited resources, it is more important to focus on interventions that are proven to be effective and can be sustained over time [1, 8]. Vitamin D as part of an individualized approach for patients with vitamin D deficiency or at risk for such deficiency may be beneficial. The value of vitamin D for the population-wide prevention of asthma has not yet been sufficiently established. Future trials therefore should not only measure the change in serum 25(OH)D concentrations but also other relevant outcomes, as well as the safety, costs, availability and use of health care resources [8, 14].

Directions for a Personalized Approach

The hypothesis that the effects of vitamin D supplementation in asthma are influenced by baseline 25(OH)D levels, by the different biological asthma phenotypes and by disease severity must be investigated in further studies, ideally in prospective trials [8, 14, 15].

Results from future studies should be reported for different patient subgroups based on their baseline 25(OH)D levels [8, 15]. Also, a standardized asthma severity and asthma control score should be used in adult patients. Also, the type of vitamin D that was used for supplementation (cholecalciferol versus calcifediol) should be reported, because of the different pharmacokinetic properties, results from studies using one of these vitamin D forms can not automatically be transferred to the other form [11]. Trials should be sufficiently powered, have sufficient follow-up, and use relevant clinical endpoints such as severe exacerbations requiring systemic steroids, emergency department visits, hospitalizations, validated asthma control scores and measures of quality of life. Changes in serum 25(OH)D can be used as an indicator of intervention exposure but are not good surrogate markers for clinical endpoints [8, 16]. Furthermore, details on the used vitamin D dosages, on the supplementation schedule, on patient compliance with the on the asthma treatment the patients are on as well as on adverse events should be reported in a standardized manner in order to allow for comparison between studies [8, 14].

Why Meta-Analyses Reach Divergent Conclusions

There are several reasons why results from meta-analyses can differ even when the same RCTs are included. These reasons include differences in the definition of an asthma exacerbation, how events are counted, the follow-up period, the age of participants (children and/or adults), the type of vitamin D, and the baseline 25(OH)D concentration of participants [8, 14, 15]. Also, the outcome measure of interest can differ and therefore results cannot be considered equivalent (e.g. the proportion of participants with at least one exacerbation versus the annual rate of recurrent asthma exacerbations per person-year). An individual participant data meta-analysis of vitamin D for the prevention of asthma exacerbations in 955 participants showed some evidence of a reduction in the rate of asthma exacerbations requiring treatment with systemic corticosteroids (IRR adjusted 0.74, 95% CI 0.56 0.97) but no evidence of a reduction in the proportion of participants with at least one exacerbation or the time to first exacerbation. Although there was some evidence of a benefit in participants with very low vitamin D status (baseline 25(OH)D <25 nmol/L), there was no evidence of interaction (p-interaction = 0.25) to indicate that the effect of treatment differed according to vitamin D status and therefore there is no evidence of benefit in people with vitamin D deficiency [15]. The subsequent Cochrane review included 20 studies with 2,225 participants in total [8]. This review found no evidence that vitamin D supplementation reduced the proportion of participants experiencing at least one asthma exacerbation requiring systemic corticosteroids (OR = 1.04; 95% CI: 0.81 1.34) [8]. It is worth noting that the results from this review may differ from the results found in the individual participant data meta-analysis by Jolliffe et al. for a number of reasons. For example, the trials included in the Cochrane review may have had different followup periods and used different definitions of the outcome of interest. In addition, the Cochrane review assessed the risk of participants experiencing at least one exacerbation, whereas Jolliffe et al. assessed the rate of participants experiencing recurrent asthma exacerbations. A recent overview of systematic reviews and metaanalyses, published in 2026, found some evidence of a reduction in the risk of asthma exacerbations in people with asthma who were given vitamin D supplements. However, there was limited or inconsistent evidence for other asthma outcomes including control of asthma symptoms, lung function and airway inflammation. As there is substantial overlap between the primary studies included in these reviews, the numerous published meta-analyses should not be taken as providing independent confirmation of any effect. Instead, the quality of the individual studies and the certainty of the findings from each should be taken into account when interpreting the secondary evidence from such reviews. Evidence for clinical use must be assessed for both quality of methods and clinical

relevance. Large, well-designed RCTs as well as high-quality systematic reviews with complete assessment of the risk of bias of the included studies should be given more weight than isolated results from subgroups, or even than pooled results from heterogeneous outcome measures [8, 14]. Statistical significance, however, must be clearly distinguished from clinical relevance, especially in small studies with wide confidence intervals.

Inflammatory Biomarkers and Clinical Outcomes

While immunological parameters can be used to assess the biological effects of vitamin D, these have to be distinguished from clinical outcomes. A systematic review and meta-analysis of 13 RCTs found no effect of vitamin D on IgE, blood eosinophil counts or FeNO. However, an increase in serum IL-10 levels was found whereas results on other inflammatory parameters were inconsistent [16]. Thus, the absence of consistent effects on the various parameters of the inflammatory response does not necessarily imply that vitamin D has no immunomodulatory effects. The various parameters are affected by many factors such as the asthma phenotype, the concomitant use of ICS, the timing of the sample, and the level of disease activity before starting treatment with vitamin D. Since individual cytokines only have limited value as markers for the asthma disease, biomarkers are best used as prespecified secondary or even as mechanistic endpoints, while the clinically relevant endpoints are used as primary endpoints.

Significance of Treatment Adherence and Confounding Factors

Vitamin D in asthma must be evaluated in the context of asthma management as a whole [1, 8]. Asthma can only be optimally controlled by correct diagnosis, choice of appropriate treatment, correct use of inhaled medications, good adherence to treatment and management of risk factors. Thus, sub-optimal asthma control does not automatically imply inadequate use of anti-inflammatory treatment and can be caused by mistakes with inhaler use, by poor adherence to treatment, by ongoing exposure to allergens or irritants, by smoking, by rhinitis, by obesity and by other concomitant diseases. These variables need to be taken into account when trying to assess the role of vitamin D in asthma [4, 8]. Severe asthma patients can be less physically active, have higher body mass index (BMI) and more comorbidities than patients with mild asthma. All of these variables can be associated with low levels of serum 25(OH)D as well as with poor asthma control. Even when adjusted for several of these variables, residual confounding is likely to remain, because some of these variables are measured with considerable error or even not at all in some studies. Of course, background asthma therapy as well as any changes in asthma treatment during the study have to be taken into account. Asthma exacerbation as well as asthma control can be influenced by the type and dose of inhaled corticosteroids (ICS) as well as by adherence to treatment with these medications [1, 8, 9]. Thus, in future studies, the background asthma treatment as well as any changes in treatment during the study should be described in more detail. Inhaler use as well as adherence to treatment with asthma medications should be assessed and reported. Any changes in the dose of asthma medications should also be documented [8, 14].

Implications for Healthcare Systems and Preventive Strategies

For interventions for asthma, not only must the biological plausibility be assessed, but also the potential public health value, the clinical relevance, the accessibility and the required resources for the intervention [1, 8]. The main priorities for the management of asthma are early diagnosis, effective treatment, patient education, the use of individual action plans for worsening symptoms and the monitoring of asthma control.

Vitamin D supplementation may be used as an add-on to other asthma treatments, but as such, it is not an alternative to conventional asthma treatment [1, 8, 14]. Therefore, the issue of preventing vitamin D deficiency has to be separated from the use of vitamin D supplements to prevent asthma attacks. The first may be justified for general health reasons in certain groups of patients, i.e. for reasons other than asthma, whereas the latter requires evidence of an effect on asthma attacks, hospitalizations and use of systemic corticosteroids.

Clinical trials currently do not provide sufficient evidence to recommend the use of vitamin D for the prevention of asthma attacks in adults with asthma. The economic evaluation of such an intervention should also take into account the opportunity cost of other asthma-related interventions that are more cost-effective (e.g. improving access to inhaled asthma medications, educating patients on the use of inhalers and supporting patients on prescribed treatment) [1].

Asthma is a common condition that affects people of all ages. Therefore, the screening of all people with asthma for vitamin D deficiency would have public health value if it were to prevent asthma attacks. However, there is no evidence to support this at present and therefore screening for vitamin D deficiency in people with asthma is not justified on the basis of their asthma alone. However, people with asthma may have other risk factors for vitamin D deficiency and therefore a targeted assessment of vitamin D status may be appropriate in these cases as part of normal clinical practice [1, 8].

The public health value of vitamin D supplementation should be further evaluated in future studies using patient-important outcomes such as quality of life, use of health care services, hospitalizations, absence from work due to illness, and health care costs in addition to measurements of vitamin D in the blood [8, 14].

Discussion

The major limitation of the current literature on vitamin D and asthma is the lack of a uniform definition of vitamin D deficiency [8, 14]. Different studies have used different thresholds to define vitamin D deficiency, such as mean serum 25(OH)D concentrations or the proportion of participants with severe vitamin D deficiency [8, 14, 15]. Thus, pooling of studies that include populations with different baseline vitamin D status may lead to clinical heterogeneity, as the response to vitamin D supplementation may depend on the baseline 25(OH)D concentration of the participants [8, 15].

The studies on vitamin D interventions for asthma differ significantly with respect to the dosage, the frequency of administration, as well as the different vitamin D compounds (cholecalciferol vs. calcifediol) [8, 11, 13]. The different vitamin D compounds are metabolized differently in the body and thus should not be compared as equivalent interventions [11]. Therefore, pooling of results of different interventions for asthma with vitamin D is not possible [8, 14].

There is considerable heterogeneity between the studies concerning the outcome measures [8, 14, 15]. Thus, the proportion of patients with at least one asthma attack, the number of asthma attacks per patient, the time to first asthma attack, treatment failure, Asthma Control Test (ACT) scores and lung function as assessed by spirometry (e.g. FEV1/FVC ratio) have been used as outcome measures in the different studies [6, 8, 9, 11, 15]. As the different outcome measures assess different aspects of asthma, they are not interchangeable. For instance, an increase in the FEV1/FVC ratio is considered positive in some studies [13], but this does not necessarily translate into better control of asthma and improved symptoms [8, 13].

There is also the problem of statistical power. Most studies are underpowered to detect rare but clinically relevant events such as severe exacerbations and hospitalizations [8, 13, 15]. There is also the problem of multiple comparisons and of subgroup analyses. This can lead to false-positive results. Therefore, it is essential to check whether the outcomes and the subgroup analyses were pre-specified, whether appropriate adjustments for multiple comparisons were made and whether the results of the studies were confirmed in independent studies [8, 14, 15].

In addition, an overview of reviews on this topic can be misleading as there is a risk of bias in the underlying primary studies. The amount of independent evidence available to support findings can be overestimated as there is overlap between included reviews. Therefore, when assessing overviews of reviews on this topic, it is also important to assess the amount of overlap between included reviews as well as the methodological quality of the included reviews [14].

Priorities for Future Research

A focused clinical question is whether correcting low vitamin D levels in adults with asthma on standard therapy can prevent severe asthma exacerbations [8, 14, 15]. Such studies would need to be large, multicenter, with sufficient statistical power to determine clinical differences between the different groups of patients, with adequate follow-up to determine the proportion of patients who experienced exacerbations requiring systemic corticosteroids and the frequency of such events [8, 15]. Secondary outcomes would include measures of asthma control, health-related quality of life, lung function as assessed by spirometry, and markers of airway inflammation such as fractional exhaled nitric oxide (FeNO) [6, 8, 16].

Study protocols and results should be made publicly available regardless of the findings to reduce the risk of publication bias. Open access to study protocols, statistical analysis plans, and anonymized participant data would facilitate independent verification and individual participant data meta-analyses [14, 15].

The clinical efficacy as well as safety and feasibility of different dosing regimens of vitamin D supplementation should be evaluated in future trials [8, 11, 13]. This should include reporting of adverse events, treatment adherence, changes in serum 25(OH)D concentrations and use of concomitant asthma medication [8, 14]. Particular attention should be paid to high-dose and bolus dosing regimens [8, 10, 13]. Future trials should also include patients with severe asthma, very low baseline vitamin D concentrations, obese patients and patients with different phenotypes of asthma, i.e. eosinophilic vs. noneosinophilic, and report results separately for adults and children [8, 14, 15].

From Laboratory Hypothesis to Clinical Applicability

Translating experimental observations into clinical recommendations requires validation across several levels of evidence [8, 14]:

- **Mechanistic level:** The proposed biological mechanisms for vitamin D in asthma are reproducible in cellular and tissue models of disease and are relevant to the human asthma pathogenesis [2, 3].
- **Observational level:** Is there an association between measured vitamin D status and clinical features of asthma after adjustment for major confounding factors? [4]
- **Interventional level:** Does RCTs of vitamin D supplementation show an effect on outcomes that are important to patients? [8, 9, 15]
- **Implementation level:** Assessing safety, cost and feasibility of an intervention within a health care system [1, 8].

The experimental studies on vitamin D receptor (VDR) signaling in immune cells and structural cells of the airways provide biological plausibility for the potential role of vitamin D in asthma [2, 3]. The observational studies, such as cross-sectional studies, are prone to confounding and even in longitudinal studies there can be residual confounding [4]. Therefore, stronger observational evidence would require repeated measurements of serum 25(OH)D, as well as detailed information on other factors such as diet, body mass index, physical activity, smoking, co-morbidity and asthma treatment [4, 8].

Stronger observational evidence would include repeat measurements of serum 25(OH)D and other factors such as diet, BMI, physical activity, smoking, other diseases and asthma treatment [4]. These factors would need to be assessed in detail and would allow for more accurate assessment of any association, however such studies would not provide evidence of causality [4, 8].

The third level of evidence is provided by the results of randomized controlled trials (RCTs) [8, 9, 15]. An increase in serum 25(OH)D levels after supplementation is not sufficient to prove the clinical efficacy of vitamin D, because it only confirms that the intervention was successful in increasing the concentration of the vitamin in the blood [8, 14].

Clinical applicability must also take into account the patient group that is being studied. It is not currently recommended that all adults with asthma should be given vitamin D supplements [1, 8, 14]. However, a more focused question could be whether there are some groups of people with asthma who would benefit from vitamin D supplementation, such as those with severe vitamin D deficiency. These people must be defined prior to the study and the deficiency must be determined by pre-specified levels [8, 15].

This phased approach of research will help to prevent early application of results that have been obtained with the use of surrogate end points and/or results that have been obtained in only a few patients [8, 13]. Moreover, it is important to distinguish the management of vitamin D deficiency in individual patients from the use of vitamin D as an asthma treatment [1, 8]. The evidence is not yet sufficient to recommend the use of vitamin D as an asthma treatment for control or prevention of exacerbations in adults with asthma [8, 14]. Therefore, for the time being, vitamin D deficiency must be assessed and treated on the basis of general clinical indications [1, 8].

Laboratory Assessment of Vitamin D Status

Serum 25(OH)D can vary greatly with season, latitude, skin pigmentation, diet, supplement use, body mass, and function of liver and kidney. One measurement may not accurately reflect long-term vitamin D status [4]. Furthermore, there is considerable inter-assay variability which makes comparisons between centers difficult [8, 14].

Studies should therefore report the season of sample collection, the type of assay used and the cut-off value used to define vitamin D deficiency [8, 14]. Vitamin D levels should be reported as mean (SD) or as percentage of population with severe vitamin D deficiency and percentage of population who reached a predefined target level of vitamin D after supplementation [8, 15].

Mean 25(OH)D levels, the distribution of values, the proportion of participants with very low levels of vitamin D and the proportion of participants who reached predefined levels after supplementation can be reported [8, 15]. A laboratory target is a biomarker and should not be confused with clinical asthma outcomes [8, 16].

Supplementation Safety and Dosing Boundaries

In addition to any benefits of vitamin D supplementation for asthma, there are also a number of potential safety concerns [8]. The vast majority of the studies on vitamin D supplementation have used very different supplementation regimens (daily, weekly, large bolus doses), and thus the results from these studies cannot be extrapolated to other dosing regimens [8, 10, 13]. Importantly, the lack of an increase in adverse events in the pooled analysis does not mean that high-dose vitamin D supplementation is safe for all patients and can be used for long periods of time. Vitamin D can cause hypercalcemia and hypercalciuria when given in excessive doses. Severe toxicity can lead to renal failure and even soft tissue calcification [8].

Conclusions

Vitamin D is of interest as a potential immunomodulator in the treatment of bronchial asthma, affecting both immune cells and structural cells of the airways via the VDR. There are a number of experimental studies that provide mechanistic insight into the potential effects of vitamin D on asthma. There are also a number of observational studies that have investigated the association between vitamin D status and various clinical features of asthma. However, none of these studies can provide evidence of a causal relationship.

The clinical studies of vitamin D supplementation for asthma have produced inconsistent results. Some of the studies reported improvement in certain parameters of asthma control or lung function but the comprehensive Cochrane review on the subject found no evidence for a reduction in severe asthma exacerbations and no other consistent clinical benefit. Therefore, the available evidence does not support the use of vitamin D as a treatment for asthma.

Vitamin D supplementation is not an alternative to inhaled corticosteroid (ICS) containing controller therapy for asthma. The use of vitamin D as an asthma-specific treatment for control and prevention of asthma exacerbations in adults with asthma is not supported by current evidence and remains to be proven in future high-quality randomized controlled trials. For now, vitamin D deficiency must be assessed and treated on the basis of general clinical indications.

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