

Vitamin D Deficiency in Childhood Asthma

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Abstract

Asthma is a common chronic respiratory disorder in children with significant morbidity and mortality. Increasing evidence suggests that vitamin D, beyond its classical skeletal functions, plays an important role in immune regulation and airway homeostasis. Vitamin D deficiency has been associated with impaired lung function, frequent exacerbations, and greater asthma severity in pediatric populations. Proposed mechanisms include modulation of T-cell responses, enhancement of regulatory T-cell activity, reduction of airway inflammation, and improved corticosteroid sensitivity. Nevertheless, existing studies report conflicting results, and the causal relationship remains uncertain. This review examines current evidence regarding the effect of vitamin D deficiency on childhood asthma severity, highlights potential immunological pathways, and identifies gaps for future interventional research aimed at optimizing asthma control and reducing disease burden in children.

Keywords: Asthma, Children, Vitamin D deficiency, Severity, Immunomodulation, Lung function, Corticosteroid resistance.

Introduction

Asthma is a chronic and heterogeneous respiratory disease characterized by airway inflammation and hyperresponsiveness (1). It affects millions of individuals worldwide and represents a significant burden due to recurrent exacerbations, persistent morbidity, and risk of mortality (1). Globally, asthma affects 1-18% of the population, with an estimated 310 million bronchial asthma patients worldwide, making it one of the most prevalent chronic conditions. The disease carries a substantial health burden, causing approximately 346,000 deaths annually across the globe. Around 14% of children worldwide have a diagnosis of asthma, making it the most common chronic respiratory disease of childhood (2).

Regional epidemiological data further illustrates the widespread nature of this condition. In Egypt, for instance, asthma prevalence has been reported as 4.8% in Egyptian infants and children aged less than 4 years across five governorates. Studies from Cairo have documented prevalence rates of 9.4% in 11-15-year-old school children, while another study reported 8.2% prevalence in children aged 3-15 years, highlighting the significant burden of pediatric asthma in different populations.

Poor asthma control is associated with numerous negative effects on children and families, including increased school absenteeism, additional educational needs, lower educational attainment, missed work days for caregivers, and substantial financial challenges (3). Clinically, asthma manifests with recurrent episodes of wheezing, dyspnea, cough, and chest tightness. These symptoms typically worsen in more severe cases and are associated with expiratory airflow limitation and progressive decline in lung function. The frequency and intensity of these respiratory symptoms increase proportionally with disease severity, significantly impacting quality of life and daily functioning.

Although the precise pathogenesis of asthma is not completely understood, it is recognized as a multifactorial condition arising from complex interactions between genetic susceptibility and environmental exposures (4). Allergic sensitization plays a central role in a large proportion of childhood cases, with allergy being associated with almost 60% of childhood and adult asthma cases. The heterogeneity of asthma is further demonstrated by its diverse phenotypes and underlying endotypes, which differ in clinical expression, inflammatory pathways, and therapeutic response (5).

The pathogenesis and clinical manifestations of asthma are remarkably complex and heterogeneous, displaying various phenotypes and endotypes. Phenotypes are distinguished to better understand asthma severity, duration of acute exacerbations, and other clinical characteristics. However, the same phenotype may encompass different pathophysiological mechanisms. Consequently, phenotypes can be reclassified according to their underlying pathogenesis using characteristic molecular biomarkers, which are termed "endotypes." This classification system provides a more mechanistic understanding of the disease and potentially guides targeted therapeutic approaches.

While spirometry remains the cornerstone of objective diagnosis and monitoring, increasing attention has been directed toward molecular biomarkers that provide insights into disease mechanisms and may guide personalized management strategies (6). Various serum biomarkers can be measured to enhance our understanding of asthma pathophysiology, offering potential for improved disease monitoring and therapeutic decision-making.

Vitamin D, traditionally known for its role in calcium and bone metabolism, has recently emerged as a factor of interest in asthma (7). Beyond its classical functions in mineral homeostasis and skeletal health maintenance, the discovery of vitamin D receptors (VDR) in multiple tissues, including the respiratory epithelium and immune cells, highlights its potential role beyond skeletal health (8). Notably, airway epithelia contain high levels of the enzyme that converts inactive vitamin D to its active form, 25-dihydroxy-vitamin D3 [25(OH)D3].

Locally activated vitamin D in the airways supports epithelial barrier integrity, enhances antimicrobial defense, and modulates both innate and adaptive immune responses (9). This active form of vitamin D contributes significantly to mucosal barrier integrity, promotes pathogen elimination, and regulates immune responses. Experimental studies suggest that vitamin D promotes regulatory T-cell activity, which in turn inhibits Th2 responses, airway inflammation, and airway hyperresponsiveness—all key components of asthma pathophysiology (10). Additionally, vitamin D has been found to enhance the efficacy of corticosteroids, potentially playing an important role in asthma treatment optimization.

Nevertheless, the relationship between vitamin D status and asthma outcomes remains controversial. Some clinical studies have demonstrated associations between low serum vitamin D and increased asthma severity, exacerbations, and impaired lung function in children, while others have failed to confirm this link or even suggested contradictory results (11). Some epidemiological studies have suggested that low serum vitamin D levels in children with asthma are associated with increased asthma exacerbations, reduced lung function, and enhanced asthma severity, whereas other studies have not observed such relationships or have even found inverse associations.

This ongoing uncertainty highlights the need for further research to clarify the potential role of vitamin D in pediatric asthma and its implications for prevention and management. Understanding the relationship between vitamin D levels and asthma control could lead to better therapeutic strategies, potentially reducing the need for multiple medications while improving overall disease management and minimizing adverse effects on child health.

Epidemiology of Childhood Asthma

Asthma represents a major global health challenge affecting approximately 300 million individuals worldwide (7). The disease demonstrates significant variability in prevalence across different geographic regions and populations. Taking the UK as an example, paediatric asthma outcomes are poor overall with considerable associated morbidity and high rates of emergency hospital admissions, and most pertinently, there are several preventable deaths each year (1). Alarmingly, the National Review of Asthma Deaths (NRAD) found that in almost all paediatric cases, there were a number of significant avoidable contributing factors and that these deaths may have been preventable.

Severe Asthma in Children

Epidemiologic studies have described specific risk factors for severe asthma and airway hyperresponsiveness. Many children with severe asthma present during school age (range 6-11 years); however, they typically report the onset of asthma symptoms earlier in childhood (first 3 years of life) compared to children with mild-to-moderate asthma (5 years mean) (14). Another significant risk factor for asthma and severe airway hyperresponsiveness may be lower lung function present shortly after birth. Infants with the lowest pulmonary function had a higher risk of current asthma and severe airway

hyperresponsiveness at 10 years of age and increased airway obstruction on lung function testing at 22 years of age compared with infants with higher lung function.

Children with severe asthma demonstrate increased airway obstruction and air trapping compared to those with milder disease. Moreover, children with airway hyperresponsiveness at 9 years of age were three times more likely to develop functional abnormalities (low postbronchodilator FEV1/vital capacity ratio) in adolescence and early adulthood, which may reflect underlying structural airway remodeling (16). In school-age and adolescent children, those with severe asthma were more likely to have increased allergic sensitization (serum IgE), more aeroallergen skin prick test responses early in life, higher prevalence of atopic dermatitis, greater bronchial hyperresponsiveness, airway obstruction, and higher fractional exhaled nitric oxide (FeNO) levels (16).

Classification of Asthma Severity

Despite numerous attempts, there is no universally accepted definition of "severe asthma," primarily due to the heterogeneous nature of the disease and the absence of standardized, validated diagnostic criteria (18). A comprehensive review of large cohorts of school-aged children with asthma identified 60 distinct operational definitions across 122 publications, highlighting significant variability in prevalence and clinical outcomes based on the definition used (19).

Traditionally, major clinical guidelines have conceptualized asthma as a single disease with a continuum of inflammatory severity. These guidelines are based on several assumptions: (1) asthma is a singular entity with variable inflammation, (2) there is a direct correlation between inflammation and symptoms, and (3) the inflammation is typically responsive to corticosteroids. Under this framework, severe asthma represents the extreme end of the disease spectrum and is characterized by high airway inflammation and symptom burden (16).

Asthma severity is categorized into three clinical grades: mild, moderate, and severe, based on symptom frequency, exacerbation history, pulmonary function, and the level of treatment required to achieve disease control. Mild asthma is characterized by symptoms less than twice per week, infrequent nocturnal awakenings, and normal lung function (FEV1 \geq 80%). Moderate asthma involves daily symptoms or nocturnal awakenings more than once per week, with lung function between 60–80% predicted FEV1. Severe asthma is defined by symptoms that persist despite adherence to high-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) therapy and appropriate management of comorbidities (21). These patients frequently experience exacerbations requiring systemic corticosteroids, hospitalizations, and reduced quality of life.

Clinical Presentation and Diagnosis

Children with asthma typically present with a symptom triad of wheeze, shortness of breath and cough. However, 'asthma' is an umbrella term used to describe this collection of symptoms and, when present, should prompt practitioners to ask, 'What type of asthma is this?' There are a number of asthma subtypes that present and respond to treatment differently (20). Wheeze is a key feature of asthma and, if not present, a diagnosis of asthma in a child is unlikely. Wheeze is an expiratory high-pitched whistle that occurs as a result of inflammation and narrowing of the small airways (21).

The prevalence of 'preschool wheeze' is an additional challenge when diagnosing asthma in young children. In the first few years of life, many children will experience wheeze, but not all will go on to develop true asthma. The diagnosis of asthma should therefore be reviewed routinely to identify true asthma and alter treatment where necessary (1). Clinical examination may be normal in children and adolescents with asthma if they present during asymptomatic periods. During acute attacks, use of accessory muscles of respiration and widespread wheeze may be present.

There is no single 'gold-standard' test that can be used to accurately diagnose asthma. In practice, a diagnosis should be made based on characteristic symptom patterns, evidence of variability in airflow limitation in the presence of airway inflammation, likelihood of alternative diagnoses and response to treatment (6). Lung function tests can be used to aid the diagnosis of asthma in children over the age of 5 years. Peak expiratory flow (PEF) and spirometry are commonly used to assess airflow obstruction and reversibility. Once a child is old enough to reliably perform lung function testing, it is recommended that this be undertaken if the diagnosis of asthma has not been previously confirmed (6).

Vitamin D

Sources and Synthesis

Vitamin D comes from two primary sources: skin exposure to ultraviolet B (UVB) rays and dietary intake (22). Dietary sources include fish oil, fish, liver, egg yolk, and dietary supplements. However, as very few foods contain vitamin D naturally, sunlight exposure remains the primary determinant of vitamin D status in humans. In a fair-skinned person, 20 to 30 minutes of sunlight exposure on the face and forearms at midday is estimated to generate the equivalent of around 2000 IU of vitamin D (22). Two or three such sunlight exposures a week are sufficient to achieve healthy vitamin D levels in summer in the UK. In the absence of adequate sun exposure, at least 800–1000 IU (20–25 mg) vitamin D per day may be needed to achieve optimal levels.

Vitamin D Metabolism

Vitamin D synthesis is initiated in the skin by solar UVB radiation (wavelength 290 to 315 nm), activating the precursor 7-dehydrocholesterol, which then circulates in the bloodstream to the liver, where it is converted into its main metabolite, 25-hydroxyvitamin D (25[OH]D), which has blood levels about 1000 times higher than the active metabolite, 1,25-dihydroxyvitamin D (1,25-[OH]₂D) (24). Until recently, it was thought that the conversion to 1,25-(OH)₂D occurred only in the kidneys. However, increasing evidence indicates that cells of most organs have the vitamin D receptor (VDR) and the capacity to synthesize 1,25-(OH)₂D locally (25). This synthesis of 1,25-(OH)₂D is dependent on serum 25(OH)D levels, the primary circulating form of vitamin D.

Definition of Vitamin D Deficiency and Insufficiency

Serum 25[OH]D is considered the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake and sun exposure, as well as the conversion of vitamin D from adipose stores in the liver (26). There are no consensus guidelines available on optimal levels of serum 25[OH]D. Vitamin D deficiency is defined by most experts as a 25[OH]D level of less than 50 nmol/L (20 ng per milliliter). 25[OH]D levels are inversely related to parathyroid hormone levels until the former reach 75 to 100 nmol/L (30–40 ng per milliliter), at which point parathyroid hormone levels begin to level off (27).

Intestinal calcium transport increases by 45 to 65% when 25[OH]D levels increase from an average of 50 to 80 nmol/L (20 to 32 ng per milliliter). 25[OH]D levels between 50–75 nmol/L (20–30 ng per milliliter) are considered indicative of vitamin D insufficiency based on the above data and their association with health outcomes. 25[OH]D levels of 75 nmol/L (30 ng per milliliter) to 100 nmol/L indicate normal vitamin D levels (27). Excessive levels or vitamin D intoxication are rare.

Prevalence of Vitamin D Deficiency

Vitamin D deficiency is one of the most common medical conditions worldwide, with more than 1 billion children and adults at risk (7). A recent survey of adults in the United Kingdom showed 60% had serum 25(OH)D concentrations below 75 nmol/L (30 ng per milliliter) in the summer months and 87% were insufficient in the winter. This survey also demonstrated a gradient of prevalence across the UK, with highest rates of insufficiency in Scotland, northern England, and Northern Ireland (26).

People living at higher latitudes are known to be at greater risk for vitamin D deficiency. Depending on the levels used to define vitamin D deficiency, 57% to 93% of the general hospital inpatient population is deficient and a recent meta-analysis concluded that use of vitamin D supplements is associated with decrease in total all-cause mortality rates (28). Children and young adults are also potentially at high risk of vitamin D deficiency; 12% of infants and toddlers from Boston, 52% of Black and Hispanic adolescents from Boston and 48% of white pre-adolescent girls in a study in Maine had 25(OH)D concentrations below 50 nmol/L (20 ng per milliliter). A large observational survey showed that 61% of children aged 1 to 21 years had insufficient levels of vitamin D (30).

The prevalence of vitamin D deficiency is also reflected in the several hundred children with rickets treated each year in the UK. However, these children represent a small proportion of all individuals with suboptimal vitamin D levels in the UK population (30).

Risk Factors for Vitamin D Deficiency

Many factors influence the amount of vitamin D that can be synthesized in the skin driven by UVB radiation. The use of sunscreen (for example, use of sun protection factor (SPF) 8 reduces vitamin D production by 92.5% and SPF 15 by 99%), darker skin pigmentation, clothing that completely covers the skin, or spending the majority of time indoors all limit the amount of light that penetrates the skin (31). Additional risk factors include exclusive breastfeeding without vitamin D supplementation, limited sun exposure, dietary restrictions, malabsorption disorders, chronic kidney or liver disease, certain medications, and seasonal variations in sunlight availability.

Immunomodulatory Effects of Vitamin D

Anti-inflammatory Properties and Immune System Interactions

The scope of vitamin D's biologic actions extends far beyond calcium and phosphate homeostasis and bone metabolism. Vitamin D receptors (VDRs) have been found in organs that are not typically involved in bone metabolism, including immune system cells such as activated T and B cells, monocytes, and antigen-presenting cells including macrophages and dendritic cells (32). Immune cells also possess the enzymatic machinery required to activate 1,25(OH)₂D locally. 1,25(OH)₂D is able to traverse the cell membrane and act within the cell by binding to VDR in the nucleus.

Effects on T-cell Responses and Th2 Immunity

Asthma is classically driven by enhanced activity of Th2 cells, which induce IgE production and promote eosinophilic airway inflammation and airway hyperresponsiveness. Research has demonstrated that vitamin D has multiple cytokine-modulating effects through several different cells of the immune system (33). In vitro studies have shown T cells to be direct targets for 1,25(OH)₂D, with a five-fold increase in VDR expression reported after activation of quiescent CD4⁺ cells. Essentially all studies using mouse or human cells agree on the capacity of vitamin D to inhibit T cell proliferation and Th1 responses (33).

Vitamin D has been shown to inhibit Th17 responses, which may be relevant in steroid-resistant airway disease. While its effects on Th2 responses are inconsistent, studies in murine models suggest that vitamin D can reduce IL-4 and IL-5 levels, limit eosinophil recruitment, and attenuate inflammation. Additionally, combining vitamin D with allergen immunotherapy post-sensitization has shown beneficial effects (35). However, other studies have shown that 1,25[OH]D₃ administration to mice had no effect on the severity of allergic airway disease induced by ovalbumin, and that VDR knockout mice failed to develop allergic airway disease, leading authors to conclude that vitamin D was required for the generation of Th2-driven inflammation in the airways (22).

Vitamin D deficiency may contribute to structural lung changes and impaired function. In vitro, 1,25[OH]D₃ was found to inhibit Th1 and Th2 cytokines, though very high doses may paradoxically enhance Th2 responses. Similarly, in humans, a nonlinear relationship exists between serum 25[OH]D and IgE, with both low and high levels linked to increased IgE (11).

Regulatory T-cell Enhancement and Anti-inflammatory Cytokines

Vitamin D enhances the production of the anti-inflammatory cytokine IL-10 by human T cells both in vitro and in vivo, both directly and in concert with glucocorticoids. Enhancement of IL-10 synthesis by B cells by vitamin D has also been reported (37). There is further evidence for the capacity of vitamin D to promote mouse and human regulatory T cell populations, both directly and through effects on antigen-presenting cells. Regulatory T cells (Tregs) suppress the activation of the immune response that causes airway inflammation and airway hyperresponsiveness. Reduction in Tregs has been linked with glucocorticoid resistance. Vitamin D has been shown to increase the production of Tregs, and in the absence of vitamin D, the number and function of Tregs are reduced (39).

Effects on Innate Immunity and Antigen-Presenting Cells

In innate immune cells, vitamin D is generally believed to promote antimicrobial pathways and impair antigen-presenting cell function. Studies demonstrate the capacity of vitamin D to induce IL-10 production by dendritic cells and promote a tolerogenic phenotype in these cells that enhances regulatory T cell function (40). Dendritic cells present allergens and activate Th2 cells, while Tregs express the immunomodulatory cytokines IL-10 and TGF β to suppress Th2 cells directly or indirectly via dendritic cells.

Respiratory epithelial cells can also constitutively convert inactive 25(OH)D to 1,25(OH) $_2$ D, enabling high local concentrations of active vitamin D to increase the expression of vitamin D-regulated genes with important innate immune functions (41). This local conversion allows for tissue-specific vitamin D actions independent of circulating levels of the active hormone.

Vitamin D and Childhood Asthma

Multiple epidemiological studies have investigated the relationship between vitamin D status and asthma in children. A high prevalence of vitamin D deficiency (54%) and insufficiency (86%) was noted in a cross-sectional case-control study of inner-city African-American children with asthma, with significantly lower vitamin D levels in asthmatic children compared to healthy controls (42). Large cross-sectional studies have shown that low serum vitamin D levels are associated with reduced lung function in adolescents and adults (43).

A study of 1024 North American children with mild-to-moderate asthma reported a high frequency of vitamin D insufficiency (35%). Additionally, vitamin D insufficiency was associated with lower mean forced expiratory volume in one second (FEV $_1$) compared with children with sufficient levels (44). However, this study was limited by the absence of repeated vitamin D measurements over time, limiting understanding of how fluctuations in vitamin D levels over time might be relevant to the observed effects.

Despite supportive evidence, some studies have suggested that vitamin D may promote rather than ameliorate the asthmatic phenotype. Regular vitamin D supplementation (2000 IU/day) in the first year of life increased the risk of developing atopy, allergic rhinitis, and asthma when assessed at age 31 years (45). However, this study was limited by the absence of data on maternal vitamin D intake and assessment of childhood asthma or atopy. Mothers reported the frequency and dose of vitamin D supplementation and daily dose was calculated based on this information.

High-dose vitamin D supplementation during pregnancy may be linked to increased risk of eczema in infancy and asthma in later childhood, as shown in a UK study, though limitations such as low follow-up reduce its strength (46). In contrast, no link was found between cord blood 25(OH)D and asthma at age 5 in a New Zealand cohort. These mixed results may reflect differences in dose, baseline vitamin D status, and timing of exposure.

Observational studies suggest a link between vitamin D and asthma but cannot establish causality. No interventional trials have definitively confirmed whether supplementation improves asthma outcomes in those with low vitamin D status (11). It remains unclear whether deficiency contributes to asthma development or results from asthma-related behaviors such as reduced outdoor activity and sunlight exposure.

Vitamin D and Wheezing in Early Childhood

Prenatal vitamin D levels may influence fetal lung and immune development, with deficiency increasing the risk of early-life wheezing. Studies have shown that low cord blood 25(OH)D is linked to childhood wheeze, and maternal vitamin D deficiency during pregnancy is associated with a higher risk of recurrent wheezing in children by age 3 (9). Children with a diagnosis of wheezy illness had more than two-and-a-half times the incidence of rickets than age-matched controls and a 10-times higher incidence of wheezy illness when severe rickets was present (48). Chest wall compliance allowing more dynamic airway collapse might have contributed to wheezy illness.

In summary, in utero and early life vitamin D deficiency/insufficiency is associated with an increased risk of wheezing. However, association does not prove causation, and further evaluation needs to be undertaken to clarify the exact role of vitamin D in the pathogenesis of wheeze (37).

Vitamin D and Airway Remodeling

Mechanisms of Airway Remodeling in Asthma

Airway remodeling is an important feature of asthma that has been linked to steroid resistance in adults. This process involves structural changes to the airways including smooth muscle hypertrophy, subepithelial fibrosis, mucus gland hyperplasia, and epithelial damage. In vitro studies have shown that vitamin D may influence airway remodeling through a direct inhibitory effect on passively sensitized airway smooth muscle cell movement, by affecting growth and contractility, and inhibiting transforming growth factor- β (TGF β) and matrix metalloproteinases (MMPs) as well as fibroblast proliferation (49).

Vitamin D Effects on Smooth Muscle and Fibrosis

Previous studies have shown in vitro that vitamin D increases glucocorticoid bioavailability in bronchial smooth muscle cells, suggesting a further beneficial role for vitamin D in the prevention and treatment of asthma (50). These data suggest that lower vitamin D levels could lead to bronchial smooth muscle proliferation, cytokine release, and thus airway remodeling. The interaction between vitamin D and smooth muscle cells appears to be complex, with vitamin D potentially modulating both contractile responses and proliferative pathways that contribute to airway remodeling.

Vitamin D may also influence the production of extracellular matrix components and the activity of enzymes involved in tissue remodeling. Studies have shown that vitamin D can modulate the expression and activity of MMPs, which play crucial roles in the breakdown and remodeling of extracellular matrix in asthmatic airways. By regulating these processes, vitamin D may help maintain normal airway architecture and prevent the progressive structural changes characteristic of severe asthma.

Vitamin D and Corticosteroid Resistance

Airway inflammation is a key component of asthma, and inhaled glucocorticoids are the most effective anti-inflammatory treatments available. However, glucocorticoid resistance or insensitivity in some patients with asthma represents an important barrier to effective treatment and accounts for significant healthcare costs (51). The molecular mechanisms of glucocorticoid resistance in children are unclear, and there is no accepted definition of steroid resistance. Congenital steroid resistance from mutations in the corticosteroid receptor is rare. Acquired steroid resistance is a spectrum and can be overcome by high doses, albeit at the risk of increased side effects (39).

Regulatory T-cells and Vitamin D in Steroid Response

Regulatory T cells express the immunomodulatory cytokines IL-10 and TGF β to suppress Th2 cells directly or indirectly via dendritic cells. Reduction in Tregs has been linked with glucocorticoid resistance. Vitamin D has been shown to increase the production of Tregs, and in the absence of vitamin D, the number and function of Tregs are reduced (52). Glucocorticoids in vitro induce IL-10 synthesis, and CD4⁺ T cells stimulated in the presence of glucocorticoids show a dose-dependent induction of IL-10 synthesis.

CD4⁺ T cells from steroid-resistant adult asthmatics fail to demonstrate increased IL-10 synthesis following in vitro stimulation in the presence of glucocorticoids, suggesting that induction of IL-10 is an important part of the anti-inflammatory effect of glucocorticoids. This steroid-induced IL-10 synthesis was overcome by the addition of vitamin D to T cell culture, and more strikingly, in a small pilot study, ingestion of vitamin D by three steroid-resistant adult asthmatic patients enhanced their response to dexamethasone for the induction of IL-10 in vitro (53). Thus, vitamin D could potentially increase the therapeutic response to glucocorticoids in steroid-resistant asthmatics.

Molecular Mechanisms of Enhanced Steroid Sensitivity

Another mechanism of glucocorticoid resistance involves the ability to regulate inflammatory gene expression and glucocorticoid receptors. In vitro, physiologic concentrations of vitamin D added to dexamethasone significantly enhanced MKP-1 expression in peripheral blood mononuclear cells compared with dexamethasone alone, suggesting that the addition of vitamin D could decrease the dexamethasone dose requirement for steroid response by more than 10-fold (54). This

finding has important clinical implications, as it suggests that vitamin D supplementation might allow for lower corticosteroid doses while maintaining therapeutic efficacy, potentially reducing steroid-related side effects.

Interventional trials with vitamin D will identify whether experimental *in vitro* evidence suggesting a steroid-enhancing function in steroid-refractory asthma will correlate with clinical benefit (54). The potential for vitamin D to restore steroid sensitivity in resistant patients represents a promising therapeutic avenue that requires further investigation in pediatric populations.

Vitamin D and Asthma Exacerbations

Viral Infections and Asthma Pathophysiology

Viral respiratory infections are a common cause of asthma exacerbations in children and adults. Increasing evidence suggests that viruses cause more than simple respiratory infections, with rhinoviruses shown to enhance allergic airway inflammation in mouse models (55). In humans, rhinovirus infection induces airway inflammation, increases asthma exacerbation severity, and results in more severe infections in asthmatics compared to normal subjects. There is emerging evidence that low serum vitamin D levels are associated with more respiratory infections, especially among patients with asthma, and with increased asthma severity.

Antimicrobial Effects and Innate Immune Enhancement

Vitamin D appears to act on innate immune cells to inhibit their inflammatory activity and capacity to prime adaptive immune responses, while also promoting direct antimicrobial functions. Emerging evidence indicates that vitamin D-mediated effects on innate immunity, particularly through enhanced expression of the human cathelicidin antimicrobial peptide (hCAP-18), are important in host defense against respiratory tract pathogens (56). hCAP-18 enhances microbial killing and acts as a chemoattractant for neutrophils and monocytes. Other antimicrobial products regulated by vitamin D include cationic peptides and defensin- β 2 and 4.

In vitro, the induction of hCAP-18 in respiratory epithelial cells by vitamin D enhances antimicrobial activity against respiratory pathogens (56). A prospective cohort study that measured serial concentrations of vitamin D in 198 healthy adults observed that individuals with 25(OH)D concentrations > 95 nmol/L (38 ng/ml) had a two-fold reduced risk of acute viral respiratory tract infections (57). This protective effect appears to be particularly important in individuals with underlying respiratory conditions like asthma.

Clinical Evidence from Intervention Studies

The association of vitamin D with asthma exacerbations triggered by acute respiratory infections is supported by intervention trials demonstrating decreased respiratory tract infections in children receiving vitamin D supplementation. A double-blind, placebo-controlled clinical study assessed the effect of vitamin D supplementation from September to July on asthma symptom score, lung function, and the number of exacerbations in children (aged 5-18 years) with newly diagnosed asthma (58). Despite the lack of any significant differences between the study groups regarding the absolute changes of vitamin D levels, the number of children with decreased 25(OH)D levels were significantly lower in the group treated with vitamin D (500 IU cholecalciferol) in addition to inhaled corticosteroids than in the control group treated with inhaled corticosteroids alone.

Vitamin D supplementation decreased the number of asthma exacerbations triggered by acute respiratory tract infections. Even though the dose of vitamin D was inadequate to increase serum 25(OH)D levels significantly, clinical benefits were observed (58). In another multi-center, randomized, double-blind placebo-controlled clinical trial in Japanese school children, vitamin D supplementation appeared to have a stronger effect in the sub-cohort with underlying asthma. Vitamin D supplements (1200 IU daily for 4 months) led to a relative risk reduction in asthma exacerbations of 93% compared with children given placebo (59). These findings suggest that even modest vitamin D supplementation may provide clinical benefits in reducing asthma exacerbations, particularly those triggered by respiratory infections.

Vitamin D Receptor Polymorphisms and Asthma Risk

Genetic studies have provided additional evidence linking vitamin D metabolism to asthma susceptibility. Vitamin D receptor (VDR) polymorphisms have been associated with asthma susceptibility, particularly variants located on chromosome 12q13–23 (60). These genetic variations may influence how individuals respond to vitamin D supplementation and could explain some of the heterogeneity observed in clinical studies. The identification of specific VDR polymorphisms associated with asthma risk supports the biological plausibility of vitamin D's role in asthma pathogenesis.

Vitamin D Binding Protein and Immune Modulation

Additionally, vitamin D binding protein (VDBP), which modulates immune responses including macrophage activation and neutrophil chemotaxis, further supports the connection between vitamin D metabolism and airway inflammation (60). VDBP serves not only as a transport protein but also as an immune modulator, with specific isoforms potentially influencing the bioavailability of vitamin D and its immunomodulatory effects. Understanding these genetic factors may help identify children who are most likely to benefit from vitamin D supplementation as an adjunctive therapy for asthma.

Biomarker Relationships and Dose-Response Effects

In humans, a nonlinear relationship exists between serum 25[OH]D and IgE levels, with both low and high levels linked to increased IgE concentrations (11). This U-shaped relationship suggests that optimal vitamin D status may exist within a specific range, and that both deficiency and excess could potentially have adverse effects. This finding highlights the importance of achieving optimal rather than maximal vitamin D levels and suggests that therapeutic interventions should aim for physiological sufficiency rather than supraphysiological concentrations.

Pharmacological Management Considerations

The pharmacological management of asthma involves maintenance and reliever therapies, with the treatment aim being that no reliever therapies are required. A stepwise approach to asthma management is encouraged, and pharmacological management varies based on age, symptom control, and national guidelines used (23). Given the potential interactions between vitamin D and corticosteroid responsiveness, vitamin D status assessment may become an important component of comprehensive asthma management.

Current GINA guidelines recommend dual ICS and short-acting beta-2 agonist (SABA) therapy to children over the age of 5, with SABA monotherapy now only recommended for children aged 5 or less due to associations with asthma mortality when used as monotherapy in older children (20). The potential for vitamin D to enhance corticosteroid sensitivity could influence these treatment algorithms, particularly in children with difficult-to-control asthma or those requiring high-dose corticosteroids.

Non-pharmacological Management and Prevention

Non-pharmacological aspects of asthma management include providing education on modifiable risk factors and comorbidities to caregivers and conducting annual asthma reviews to assess control and future risk. Education regarding modifiable risk factors, such as smoke exposure, domestic pollutants, and obesity, should be given (23). Vitamin D deficiency represents another potentially modifiable risk factor that could be addressed through dietary counseling, lifestyle modifications to increase safe sun exposure, and supplementation when appropriate.

All young people with asthma should have asthma reviews at least annually, focusing on current symptom control and management, previous attacks, triggers, modifiable risk factors, and personal asthma action plans (PAAPs) (23). These reviews provide opportunities to assess vitamin D status and consider supplementation as part of comprehensive asthma care.

Self-management and Patient Education

Self-management aspects of pediatric asthma management include asthma education and PAAPs. PAAPs are written documents given to young people and/or caregivers that advise them on day-to-day asthma management and what to do in

the event of an attack. Action plans should be created with patient/caregiver input, shared with relevant individuals, and should be reviewed and updated regularly (23). The 2018 Annual Asthma Survey found that over 50% of children with asthma in the UK had no PAAP, highlighting large gaps in education.

Diet and exercise are additional important self-management aspects within pediatric asthma care. A number of short-term exercise interventions have demonstrated improvements in lung function and symptom control. Healthy eating interventions can help reduce body mass index and improve quality of life for both young people and their caregivers (21). Education about vitamin D sources, including safe sun exposure and dietary sources, could be incorporated into these lifestyle counseling sessions.

Predictors of Severe Asthma and Life-threatening Attacks

Several features have been shown to increase the likelihood of future severe attacks, and particular attention should be given to these factors during asthma reviews. The strongest risk factor for a future asthma attack is a personal history of a previous attack. One large systematic review and meta-analysis found that children with a recent history of emergency department attendance with an asthma attack were up to 5.8 times more likely to have another emergency department attendance and up to three times more likely to be admitted to the hospital with a future asthma attack (4).

Frequent use of short-acting beta-agonist (SABA) reliever therapy suggests poor control of asthma symptoms. If asthma symptoms are well controlled, no more than two SABA inhalers should be required annually. The UK National Review of Asthma Deaths found that excess SABA prescription and use were prominent in individuals who died of asthma attacks, with around 40% having been prescribed 12 or more SABA inhalers in the 12 months before death (23).

Post-attack Management and Review

Asthma attacks should be viewed as never events, and it is essential that a post-attack review is conducted to review asthma maintenance treatment, as this is likely to be suboptimal. Failure to review patients post-attack and to alter treatment where appropriate is likely to predispose to future attacks, which could be life-threatening (23). Current NICE quality standards state that all individuals hospitalized with an asthma attack should receive a follow-up review in primary care within two working days of discharge. However, the 2018 National Asthma Survey found that 64% of respondents had no primary care follow-up post-attack.

During post-attack reviews, assessment of vitamin D status could be considered, particularly in children with recurrent exacerbations or those with difficult-to-control asthma. Given the potential role of vitamin D in reducing respiratory infections and enhancing corticosteroid sensitivity, correction of deficiency might represent an important adjunctive intervention in preventing future exacerbations.

Future Directions in Pediatric Asthma Care

The management of pediatric asthma is evolving with developments in technology and service structure. The growing use of technology in asthma care has huge potential to improve clinical outcomes. Smartphone applications can be used to provide medication reminders to users, which has been shown to increase ICS adherence. Applications can also provide educational content to young people and caregivers and store PAAPs (23).

'Smart' inhalers, not to be confused with SMART (single maintenance and reliever therapy) inhalers, are devices that can provide audio reminders to users and record when they are used. One pediatric study found that the use of smart inhalers increased treatment adherence to 84%, compared with 30% in the control group (23). These technological advances could potentially be integrated with vitamin D monitoring and supplementation reminders to provide comprehensive digital health solutions for pediatric asthma management.

In the UK, regional diagnostic hubs for asthma care have been recommended in NHS England's Long Term Plan. Implementation of diagnostic hubs is hoped to result in earlier and more accurate asthma diagnoses by improving access to objective testing and specialized interpretation. Hubs are designed to improve asthma outcomes by enabling most appropriate treatment initiation and monitoring (6). These specialized centers could also facilitate comprehensive

assessment of nutritional factors, including vitamin D status, and provide coordinated care that addresses both pharmacological and non-pharmacological aspects of asthma management.

The recognition of asthma as a heterogeneous disease with multiple phenotypes and endotypes has led to increased interest in personalized treatment approaches. Key endotypes include 'type 2-high' and 'type 2-low' asthma, with type 2-high asthma typically responding well to inhaled corticosteroid treatment and being characterized by eosinophilic airway inflammation, raised IgE, and elevated FeNO levels (5). Understanding how vitamin D status interacts with different asthma phenotypes could help identify subgroups of patients most likely to benefit from vitamin D supplementation.

A number of biologic agents are now available for the management of severe pediatric asthma under specialist supervision, and their use varies based on asthma endotypes (5). Future research should investigate whether vitamin D status influences response to these targeted therapies and whether vitamin D supplementation could enhance their efficacy or reduce the need for more intensive interventions.

Supplementation Strategies and Safety Considerations

While specific guidelines for vitamin D supplementation in asthmatic children remain to be established based on robust clinical trial evidence, current recommendations for general pediatric populations can provide guidance. The American Academy of Pediatrics recommends 400 IU daily for infants and children, while some experts suggest higher doses (800-1000 IU daily) may be needed to achieve optimal levels in deficient individuals (26,27).

Safety considerations include the risk of vitamin D toxicity with excessive supplementation, though this is rare with recommended doses (27). Regular monitoring of 25(OH)D levels may be appropriate in children receiving high-dose supplementation or those with conditions affecting vitamin D metabolism. Healthcare providers should also consider potential interactions between vitamin D supplementation and other medications used in asthma management (31).

Integration with Standard Asthma Care

Vitamin D assessment and supplementation should complement, not replace, evidence-based asthma therapies (23). The primary focus should remain on appropriate use of controller medications, trigger avoidance, and adherence to prescribed treatments. Vitamin D supplementation should be viewed as a potentially beneficial adjunctive intervention that may enhance the effectiveness of standard treatments, particularly in children with documented deficiency (58,59).

Education of patients and families about vitamin D should include information about natural sources (sunlight exposure and dietary sources), the potential benefits in asthma management, and the importance of adherence to supplementation regimens (22,23). This education should be integrated into broader asthma self-management programs and reinforced during regular asthma reviews (23).

Conclusion

Vitamin D deficiency is highly prevalent in children with asthma and exhibits strong biological plausibility for influencing disease severity through immune modulation, corticosteroid sensitivity enhancement, and antimicrobial defense mechanisms. While cross-sectional studies consistently demonstrate associations between low vitamin D status and worse asthma outcomes, limited and conflicting intervention trials prevent definitive conclusions about causality. Given the low risk of supplementation and high deficiency prevalence in asthmatic children, vitamin D assessment warrants consideration in comprehensive asthma management, particularly for severe cases, though it should complement rather than replace evidence-based therapies. Well-designed randomized controlled trials stratified by asthma phenotype and baseline vitamin D status are urgently needed to establish optimal therapeutic approaches for this potentially modifiable risk factor.

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