

Review Article

Exploration of Vitamin D Supplementation Adjuvant Therapy for Childhood Asthma and the Best Treatment Options

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Abstract: Vitamin D not only promotes the health of human bones and muscles but also has an important impact on the metabolism of extraskelatal tissues. As a steroid hormone, vitamin D possesses important physiological functions, including cell differentiation and proliferation and immune regulation. Research has shown that vitamin D insufficiency (VDI) or vitamin D deficiency (VDD) can make children susceptible to asthma. Vitamin D has important immunoregulatory functions associated with preventing the occurrence of asthma or the worsening of its symptoms, improving lung function and enhancing glucocorticoid (GCS) action. An increasing number of randomized controlled intervention studies have confirmed that vitamin D affects the occurrence and development of asthmatic diseases. In recent years, accumulating laboratory and clinical research has supported the use of vitamin D as an adjuvant treatment for asthma and has achieved good clinical results. But the clinical outcome of vitamin D in the treatment of asthma is not as impressive as experimental studies. In addition to the complexity of clinical research, it may be related to clinical application methods. In order to combine theory with clinical practice, focused on exploring and selecting the most effective vitamin D adjuvant treatment of asthma, and comprehensively optimizing and applying these methods is beneficial to improve the therapeutic effect. However, there are different opinions regarding the results of the studies.

Keywords: Vitamin D, VDD, Asthma, Children, Vitamin D Adjuvant Therapy

1. Introduction

Pediatric asthma is a common disease in children. Shortness of breath, chest tightness, asthma, and repeated coughing often occur or worsen at night and/or in the morning. The

prevalence rate of asthma has risen in recent years. Asthma affects approximately 300 million people worldwide [1].

Epidemiological studies and meta-analyses over the past 20 years have shown that VDD in children can increase their risk of asthma. VDD in pregnant women has also been associated

with increased recurrent wheezing in their offspring [2].

Vitamin D, as a steroid hormone, also has a great influence on the metabolism of extraosseous tissues. Research has shown that vitamin D regulates more than 5% of human genes, regulates the expression of 291 genes in leukocytes, and participates in more than 160 different biological metabolic pathways, inducing physiological responses in 36 different cell types [3, 4]. Among these genes, those related to the human immune response are an area of concern. On the one hand, most immune cells, including monocytes, macrophages, dendritic cells (DCs), T lymphocytes and B lymphocytes, can express vitamin D receptor (VDR). In addition, localized 25 (OH) D can be converted to active 1, 25 (OH)₂D in immune cells. VDR and vitamin D signals together promote DC and Tregs differentiation and reduce Th17 cellular responses and inflammatory cytokine secretion. Therefore, vitamin D has immunomodulatory and anti-inflammatory effects.

Whole-genome microarray studies have found for the first time that vitamin D supplementation affects many important regulatory and metabolic pathways, confirming the potential effect of vitamin D on DNA repair, stress response, and immune regulation [4]. Genetic studies have also found that genetic polymorphisms in certain VDRs and vitamin D binding proteins (VDBPs) increase asthma susceptibility [5-8].

In the case of VDD, adaptive and innate immune system cells as well as upper respiratory tract cells promote inflammatory responses and produce corresponding cytokines [9], which can be alleviated by vitamin D supplementation. Therefore, the multiple biological effects of vitamin D and VDD may have momentous effects on the pathogenesis and severity of asthma, such as reducing lung function, increasing airway hyperresponsiveness and reducing the effects of GCS treatment [10, 11]. The immunomodulatory function of vitamin D can increase the production of antimicrobial peptide (AMPs) such as cathelicidin. These immunomodulations prevent bacterial/viral infections, reduce asthma attacks, improve airway function, increase responsiveness to GCS and have clinical benefits [12]. Research has shown that vitamin D intake in GCS-resistant asthma patients can enhance the response to dexamethasone-induced IL-10 synthesis. IL-10-secreting Tregs may have potential for treating asthma and allergic diseases [13].

Recent research has shown that vitamin D not only prevents asthma but also serves as an adjunct treatment for asthma [2, 14, 15]. This article describes the negative effects of VDD on asthmatic children and some important advances in the treatment of asthma in children with vitamin D in recent years and explores how to choose the best treatment to achieve good results. The results of clinical trials have also led to some different conclusions [16, 17].

2. The Effect of VDD on the Incidence of Pediatric Asthma

2.1. Disputes About Vitamin D Sufficiency (VDS), VDD, VDI and Standards

What are the baseline levels of VDS, VDD and VDI? The

dispute still exists. The old standard for VDD [25 (OH) D <11 ng / mL] can only prevent the typical imaging findings of rickets, and normal bone metabolism indicators can be maintained with 25 (OH) D ≥30 ng / mL. Vitamin D (as a steroid hormone) is needed to maintain the mineral balance and other important physiological functions, such as the regulation of immunity and cell differentiation and proliferation. Therefore, determining whether vitamin D is sufficient based solely on calcium homeostasis or bone turnover does not reflect the full potential of vitamin D. Intestinal calcium absorption, PTH content and the content of 25 (OH) D should also be considered [18].

The American Endocrinology Society defines 25 (OH) D 30 ng / mL as VDS, less than 20 ng/ml as VDD, and 21-29 ng/mL as VDI [19]. The American Institute of Medicine believes that 20 ng/mL 25 (OH) D can meet the demands of 97.5% of people [20].

The Italian vitamin D consensus defines VDS as ≥30 ng/mL, VDI as 20-29 ng/mL, VDD as <20 ng/mL, and severe inadequacy as <10 ng/mL [21].

The Poland Vitamin D Supplementary Guidelines use the following definitions: toxic concentration: > 100 ng/mL; high concentration: > 50-100 ng/mL; adequate concentration: > 30-50 ng/mL; inadequate concentration: > 20-30 ng/mL; VDD: > 10-20 ng/mL; and severe VDD: 0-10 ng/mL [22].

The European Endocrine Society Guidelines (2011) indicate that normal 25 (OH) D is 30-50 ng/mL and that the minimum effective concentration varies from tissue type to tissue type. Some studies have summarized the lowest effective 25 (OH) D level relevant to the risks of bone and nonskeletal systemic diseases. Bone system diseases are defined according to the following 25 (OH) D levels: rickets: 10 ng/mL; osteoporosis: 20 ng/mL; fracture: 20 ng/mL; nonskeletal diseases, such as early death: 30 mg/mL; depression: 30 ng/mL; diabetes mellitus: 32:mg/mL; cardiovascular diseases: 32:mg/mL; RTI (respiratory tract infection): 38 ng/mL; falls: 38 ng/mL; and cancer: 40 mg/mL [23].

2.2. The Impact of VDD on Asthmatic Children

In 2017, the National Health and Nutrition Survey was completed in the United States. Lung function, 25 (OH) D level and asthma were surveyed in adults and children, and asthma in adults and children was found to be associated with VDD. VDD is also related to decreases in forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) in children and adults. It has also been found that when VDD is reduced, the prevalence of asthma is also reduced [24].

In a meta-analysis, the authors analyzed the relationship between VDD and VDI and pediatric asthma risk. Of these studies, 15 involved 3, 424 patients with VDD. Another 10 studies analyzed 2, 756 patients with VDI. The authors concluded that VDD is evidently related to pediatric asthma risk. VDI was also evidently related to pediatric asthma risk. The authors believed that VDD and VDI increase the risk of pediatric asthma [25].

A study showed that 93% of asthma patients have a reduced

25 (OH) D concentration. Of these, 17.5% had VDI, and 75.5% had VDD. In the patients with VDD, the severity of asthma was exacerbated, and more GCS treatment was needed [26]. Arikoglu *et al.* showed that VDD was associated with an enhanced risk of asthma attack and symptom deterioration in children. Research confirms that a 1 ng/mL reduction in the vitamin D concentration predicted a 1.2-fold increase in the risk of asthma attacks [27].

VDD can exacerbate the oxidative stress response, which can be confirmed by increased DNA damage and reactive oxygen species (ROS) in patients with severe asthma. Patients with low vitamin D levels have lower FEV1 than patients with VDS. Vitamin D supplementation increases the GCS response, reduces oxidative stress, and reduces the lipopolysaccharide (LPS)-mediated stimulation of airway epithelial ROS release and DNA damage, suggesting that VDD may have a large role in the acute exacerbation of asthma. Oxidative stress promotes airway inflammation by activating proinflammatory genes to promote the release of airway hyperresponsiveness mediators, ultimately leading to decreased lung function and increased disease severity [28]. A 20-year prospective study in Denmark confirmed that low 25 (OH) D levels are interrelated with decreased lung function (FEV1 and FVC) and increased risk of chronic obstructive pulmonary disease (COPD) [29].

3. Effect of Vitamin D Supplementation on Asthmatic Children

To date, there have been two well-known prenatal vitamin D supplementation trials, the Vitamin D Antenatal Asthma Reduction Trial (VDAART, N = 806) and the Copenhagen Prospective Studies on Asthma Childhood (COPSAC 2010, N = 581). In the two trials, expectant mothers were randomly divided into two high-dose vitamin D groups that received vitamin D 2400 IU/day and 4000 IU/day and a placebo group that received vitamin D 400 IU/day. The endpoint was the occurrence of asthma / recurrent wheezing in offspring at ages 0 to 3 years. The results showed that the intake of vitamin D in expectant mothers can reduce the risk of asthma or repeated wheezing in their child by 26%. If an expectant mother's 25 (OH)D level was ≥ 30 ng/mL at the beginning of the trial, the impact of vitamin D was the strongest (the risk was reduced by 46%). In terms of prenatal care strategies, consideration should be given to increasing the 25 (OH) D concentrations of expectant mothers to avoid or reduce the risk of wheezing or asthma in their offspring [2, 30]. The vitamin D dose may have been insufficient in both trials. Although the best maternal 25 (OH) D concentrations for fetal immunity and lung development are unknown, they may reach 40-60 ng/mL. In both trials, the intake of vitamin D markedly enhanced the 25 (OH) D level; however, only 75% of the subjects in the VDAART and 82% of subjects in the COPSAC2010 achieved or exceeded 25 (OH) D concentrations of 30 ng/mL.

Insufficient doses of vitamin D may have reduced the positive effects observed in both trials. Low 25 (OH) D may not reverse the changes in lung development caused by VDD

before vitamin D supplementation. Taking vitamin D can reduce the risk of asthma or recurrent wheezing in the child of expectant mothers, which makes vitamin D a promising nutrient for the prevention of immune-mediated diseases [2, 30]. Another meta-analysis also showed that prenatal supplementation with vitamin D evidently decreased the risks of recurrent wheezing or asthma in offspring [31].

Epidemiological studies confirmed that if the level of 25 (OH) D in the cord blood of newborns is low, it may increase the risk of asthma / repeated wheezing in the offspring of pregnant women [32].

Majak *et al.* conducted a six-month trial of 48 children aged 5-18 years (mean age 11.5 years) who had asthma and were allergic to house dust mites. The children were divided into the vitamin D (500 IU/day) + inhaled budesonide (800 μ g/day) group (n = 24) or the inhaled budesonide (800 μ g/day) group (n = 24). The study showed that vitamin D supplements not only prevented VDD but also reduced acute asthma attacks caused by acute respiratory tract infections (ARTI) [33, 34].

In 2016, a Japanese study examined the impact of vitamin D intake (800 IU per day) versus placebo on 89 asthmatic children. Eighty-nine children with asthma were divided into the placebo group (PG) (n = 35) and vitamin D group (VDG) (n = 54). Two months later, the Global Asthma Prevention Initiative (GINA) asthma control standard was used for evaluation, and asthma control was evidently worse in the PG than in the VDG (p = 0.015). The asthma control test (minor outcome) score also showed evident improvement in the VDG (p = 0.004), and the difference was still evident after 6 months (p = 0.012). Among the patients with PEFR < 80%, the VDG (8/54, 15%) had evidently lower values than the PG (12/35, 34%) (p = 0.032). The authors believe that the addition of vitamin D to asthma treatment regimens can improve asthma in children [35].

A cross-sectional analysis showed that most children suffer from VDD at birth, suggesting that expectant mothers may suffer from VDD and that improving the 25 (OH) D status of expectant mothers may have additional benefits. Eliminating childhood VDD can at least prevent asthma [36]. Pojsupap *et al.* reported that vitamin D 500-2000 IU/day was found to prevent asthma exacerbations [37].

One study confirmed that enhancing levels of 25 (OH) D in obese urban asthma patients could reduce the severity of asthma symptoms caused by high particulate matter 2.5 (PM_{2.5}). Indoor PM_{2.5} can aggravate the adverse respiratory response of children with VDD. Vitamin D supplementation can reduce asthma attacks caused by indoor air pollution [38].

4. Recommendation for Vitamin D Supplementation

Thus far, experimental studies on vitamin D have yielded convincing results. Although the results of randomized clinical controlled trials are not as impressive as the results of these experimental studies, increasing evidence confirms that the addition of vitamin D to standard therapies for childhood

asthma is a beneficial measure [14, 40].

4.1. The Right Time to Supplement with Vitamin D

Some researchers believe that vitamin D treatment should begin as soon as laboratory test results confirm VDD (< 20 ng/mL). Vitamin D should be supplemented for 1-3 months, depending on the child's age, weight and residential zone [41]. If the 25 (OH) D concentration does not reach 30 ng, doses can be increased to 1000 IU/day for newborns; 2000-3000 IU/day, for infants and 3000-5000 IU/day for children aged 1-18 years until good clinical results are achieved [42]. The study found that when neonatal cord blood 25 (OH) D is < 30 ng/mL, ARTI is prone to occur within two years of birth, indicating that vitamin D needs to be supplemented from birth [43]. To prevent the risk of asthma in the offspring of pregnant women, vitamin D should be supplemented from the beginning of life. It is a misunderstanding to believe that the impact of vitamin D is confined only to the alveolar phase of embryonic lung development. In actuality, Vitamin D plays a considerable role in the early morphogenesis of the fetal lung.

Therefore, in the COPSAC 2010 study, vitamin D supplementation for expectant mothers started at 10 to 18 weeks of gestation, while in the VDAART study, vitamin D supplementation for expectant mothers started at 22 to 26 weeks of gestation. This timing seems slightly late, and it may not have achieved the greatest impact of vitamin D. In addition, vitamin D also affects human fertility; therefore, adequate vitamin D intake before pregnancy helps optimize the implantation of fertilized eggs. Vitamin D affects the development of the embryonic lung and immune system from the beginning of life [2, 31].

4.2. Suitable Dosage for Vitamin D Supplementation

The study concluded that supplementation with vitamin D 500 IU/day for children with asthma was not sufficient to increase 25 (OH) D [44]. After taking vitamin D 1000 IU/day for 12 months, only 50% of patients had a 25 (OH) D concentration > 30 ng/mL [45].

Recent studies have shown that in order to reduce the risk of asthma, vitamin D 500-2000 IU should be replenished daily [22]. The American Endocrinology Society recommends that adults take vitamin D 4000 IU/day [23]. Supplementation with vitamin D 1000 IU/day can maintain the bone health of asthma patients, especially GCS users. Therefore, taking vitamin D 2000 IU/day can promote the extraskeletal effect of vitamin D. The addition of 1500-2000 IU of vitamin D per day can increase 25 (OH) D > 30 ng/mL [20, 26]. To maximize the effect of vitamin D on gene expression, it may be necessary to supplement with more than vitamin D 2000 IU/day. Recent observations indicate that VDD patients have specific gene expression patterns and that they change significantly with increasing 25 (OH) D levels [4].

4.3. Appropriate Route Selection for Vitamin D Supplementation

In general, oral supplements are more convenient and

appropriate, and high-dose, intermittent multiple-injection medications are not recommended. Recently, a meta-analysis of 25 studies involving 10, 933 patients concluded that daily or weekly supplementation of vitamin D could prevent RTI and decrease the risk of ARTI at least once. This meta-analysis also found that only daily or weekly vitamin D supplementation could prevent ARTI and that severe VDD patients experienced the strongest protective effect, while high-dose injections could not prevent ARTI. Intermittent use of high-dose vitamin D injections should be avoided [42, 46, 47]. Research has shown that RTI can cause asthma recurrence/deterioration.

Why is the use of a bolus dose of vitamin D ineffective for preventing ARTI? The potential adverse effects of extensive fluctuations in 25 (OH) D in the circulation after bolus administration may affect the long-term regulation of the synthesis and degradation of the active 1, 25 (OH)₂D enzyme, giving rise to a reduction in the 1, 25 (OH)₂D metabolite concentration in extrarenal tissues. This effect may impair the ability of 25 (OH) D to support protective immune responses to respiratory pathogens [42, 48].

4.4. The Best Treatment Course That Produces Positive Results

Considering that the half-life of 25 (OH) D is 2-3 weeks and is affected by natural seasonal changes and infections, the treatment duration should be more than 12 months [49]. In one study, 70 immunodeficient patients and children with frequent RTIs were divided into the vitamin D intervention group (VIG) and control group (CP). The VIG received 4000 IU/day for one year.

The results showed that the VIG was significantly better than the CP in terms of infection score, antibiotic application, microbial culture status and 25 (OH) D concentration. The study also observed a time-dependent effect of vitamin D intervention, which may affect the immune function of patients for more than 6 months [50, 48].

Yadav et al. studied the therapeutic effects of vitamin D on moderate to severe asthma in children. The vitamin D group (VDG) and the placebo group (PG) were treated according to the GINA guidelines. In addition, the VDG received a monthly supplement of 60 000 IU for 6 months, while the PG received glucose powder as a placebo. The results showed that the decrease in the frequency of asthma symptoms in the VDG was significantly lower than that in PG ($P = 0.011$). PEFr increased significantly ($p=0.000$), steroid demand decreased significantly ($p=0.013$), and the number of emergency room visits decreased significantly ($P=0.015$). In the VDG, not only were the asthma symptoms controlled early, but the severity of asthma was evidently decreased over the next 6 months ($p=0.016$) [51, 49].

In short, the best course of treatment for vitamin D adjuvant therapy for asthma may take 6-12 months.

4.5. The Best Target 25 (OH) D Level After Supplementation with Vitamin D

The American Endocrinology Society recommends an

optimal 25 (OH) D concentration of 40-60 ng / mL, or at least > 30 ng / mL. It is recommended that infants take vitamin D 400-1000 IU daily, > 1- to 18-year-old children take vitamin D 600-1000 IU per day, and adults take 1500-2000 IU per day [20, 19]. VDD makes asthmatic children sensitive to RTI, and RTI can lead to an asthma attack. Children with asthma who have 25 (OH) D > 38 ng / ml are less prone to RTI [46, 45]. Children with low 25 (OH) D are prone to ARTI as lower 25 (OH) D levels are ineffective in activating AMPs mRNA and cannot induce sufficient cathelicidin production, cathelicidin can kill pathogens [46, 45]. Vitamin D supplementation reverses the induction of cathelicidin mRNA. Therefore, vitamin D levels greater than 38 ng/mL are needed to most effectively activate cathelicidin mRNA to produce sufficient levels of cathelicidin [46, 48, 45].

5. Conclusions

Epidemiological, laboratory and clinical research have found that VDD in asthmatic children may be related to increased airway inflammation, decreased lung function, worsened conditions and a poor overall prognosis. Vitamin D supplementation is a beneficial option for adjuvant asthma therapy [14, 50]. In combination with standard anti-asthma treatments, vitamin D can achieve many of the clinical benefits described below. (1) Vitamin D can help maintain the bone health of children with asthma. The combination of vitamin D and GCS can reduce bone calcium loss and benefit normal body development in asthmatic children [51]. (2) Vitamin D can reduce or avoid the occurrence of RTI, and RTI can cause asthma recurrence/deterioration. Vitamin D regulates immune function, induces the production of cathelicidin and defensins, and increases IFN γ and IL-10 levels against bacterial, viral, and fungal infections [45, 52]. (3) The use of vitamin D can enhance the GCS response. Approximately 15% of children with asthma are resistant to GCS. Vitamin D supplementation can increase IL-10 secretion and enhance the anti-inflammatory function of GCS by regulating damaged Tregs, thus reversing GCS resistance [53]. (4) Vitamin D supplementation can alleviate other side effects of GCS treatment, such as hyperglycemia, hyperlipidemia, allergies and behavioral abnormalities, in experimental rats [54]. (5) Vitamin D can provide prenatal help, and the prenatal intake of vitamin D by pregnant women can increase their 25 (OH) D concentration, which can reduce the risk of asthma/wheezing in their offspring [30]. Vitamin D supplementation is a low-risk, low-cost, convenient and practical method for the adjuvant treatment of asthma and deserves further research and promotion.

Abbreviations

AMPs: antimicrobial peptide
 ARTI: Acute respiratory tract infections
 COPD: chronic obstructive pulmonary disease

COPSAC 2010: Copenhagen Prospective Studies on Asthma in Childhood 2010

CP: control group

DCs: dendritic cells

FEV₁: forced expiratory volume in 1s

FVC: maximum vital capacity

GCS: glucocorticoids

GINA: Global Asthma Initiative

LPS: lipopolysaccharide

PEFR: peak expiratory flow rate

PG: placebo group

PM_{2.5}: Particulate matter 2.5

ROS: reactive oxygen species

RTI: respiratory tract infections

VDAART: Vitamin D Antenatal Asthma Reduction Trial

VDBPs: vitamin D binding protein

VDD: vitaminD deficiency

VDG: vitamin D group

VDI: vitamin D insufficient

VDR: vitamin D receptor

VDS: vitamin D sufficiency

VIG: vitamin D intervention group

Author Contributions

Professor of pediatrics Zhen-Dong Yang made major contributions to conception and design of the manuscript and the revision of the manuscript. All authors contributed to the literature research. Professor of Pediatrics MD Xu-Ding Sun, Associate Professor of Pediatrics Ji-Hong Wu, Professor of Pediatrics Gao-Jun Zhou, and Associate Professor Xiong Xie supported manuscript writing. Doctor Ying-Yang Xu, MD and Associate Professor MD Kai Guan made contributions to revision of the manuscript. All authors reviewed and approved the content of the submitted manuscript.

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Conflicts of Interest

The authors declare no conflict of interest

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