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Review Article

Internal Medicine Section

Clinical Effects of Vitamin D on the Control of Bronchial Asthma-Is it Relevant?

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ABSTRACT

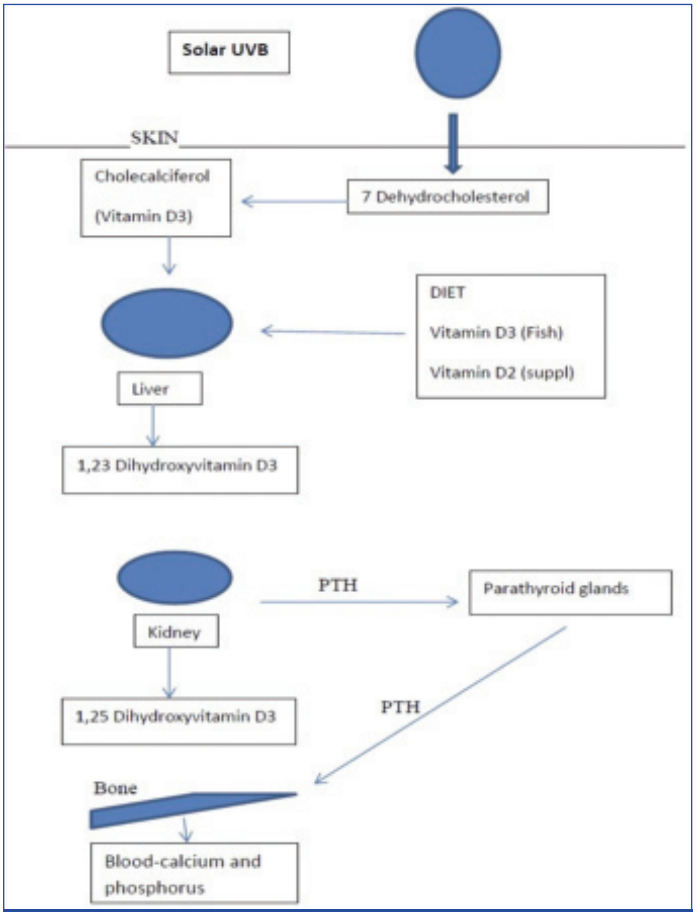
Bronchial asthma is one of the most common chronic respiratory disease worldwide, and is characterised by different phenotypic variations. Acute exacerbations in bronchial asthma are common and leads to repeated hospitalisations leading to increase in direct costs of asthma and thus preventing exacerbations should be an important consideration. Vitamin D has an immunomodulatory action and its deficiency has been associated with asthma epidemics. We hereby critically review the clinical benefits of vitamin D in the control of bronchial asthma and in exacerbations.

Keywords: Chronic respiratory disease, Clinical review, Exacerbations

INTRODUCTION

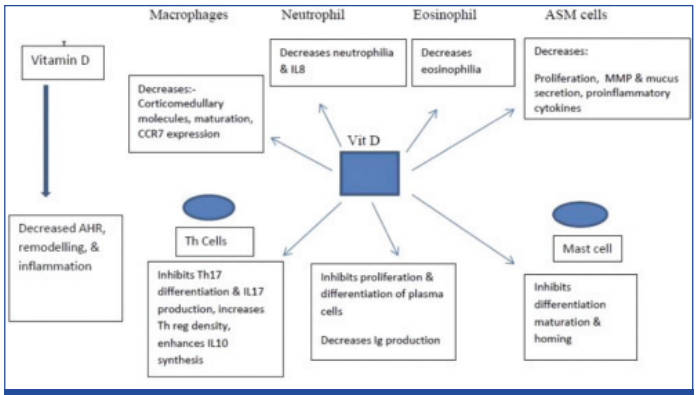
Vitamin D in Health and Disease

The first step in the synthesis of Vitamin D is from Ultraviolet (UV) light through sun exposure. Seven-dehydrocholesterol which is distributed in the skin, on exposure to the UV-B spectrum of 290-315 nm frequency, is converted to previtamin D3, which is then isomerised to Vitamin D3. Vitamin D metabolism is described in [Table/Fig-1]. Studies now indicate 1-α-hydroxylase is also present in lung epithelial cells also [1,2].



[Table/Fig-1]: Vitamin D metabolism in human body.
PTH- Parathyroid hormone

Vitamin D helps in calcium, phosphorus and bone metabolism. Deficiency causes osteoporosis, bone fractures and muscle weakness [2]. Non-skeletal actions of Vitamin D include controlling of genes responsible for regulation of cell proliferation, differentiation, apoptosis, and angiogenesis, inhibition of renin synthesis, increasing insulin production and increase in myocardial contractility. The effects of Vitamin D on various cells is illustrated in [Table/Fig-2]. Thus, deficiency is related to cancer, autoimmune diseases, osteoarthritis, diabetes mellitus, cardiovascular diseases and poor lung functions [3]. Vitamin D metabolism is also involved in the development of various allergic disorders [4].



[Table/Fig-2]: Immunomodulatory effects of vitamin D on inflammatory cells in asthma.
ASM: Airway smooth muscle; CCR7: Chemokine receptor 7; MMP: Matrix metallo proteinase; IL: Interleukin; Th: T helper; AHR: Airway hyper responsiveness; IG: Immunoglobulin; T reg: T regulatory cells

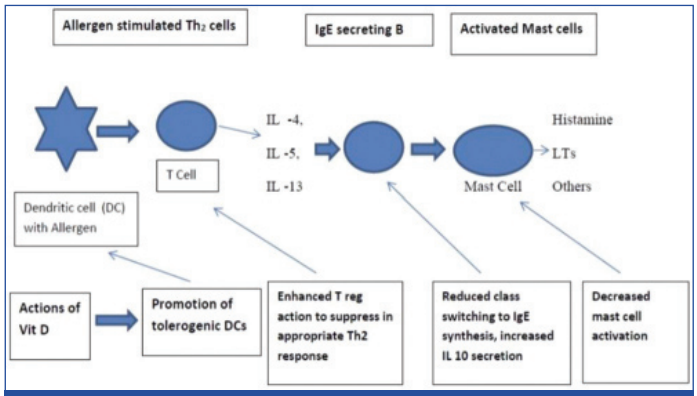
Prevalence of Vitamin D Deficiency

Hypovitaminosis D is present worldwide. A study conducted on healthy Asian Indians showed a mean serum Vitamin D levels of 9.8±.0 ng/mL, with no significant difference between men and women [5]. Another study on healthy volunteers showed a mean Vitamin D concentration of 12.3±10.9 ng/mL [6]. It is highly prevalent in pregnant females and children. Limited outdoor activity and air pollution also plays a role, with a study showing urban populations having lower levels compared to rural subjects [7]. Yet another study has shown that Vitamin D concentrations of rural subjects were significantly higher compared to urban subjects [8].

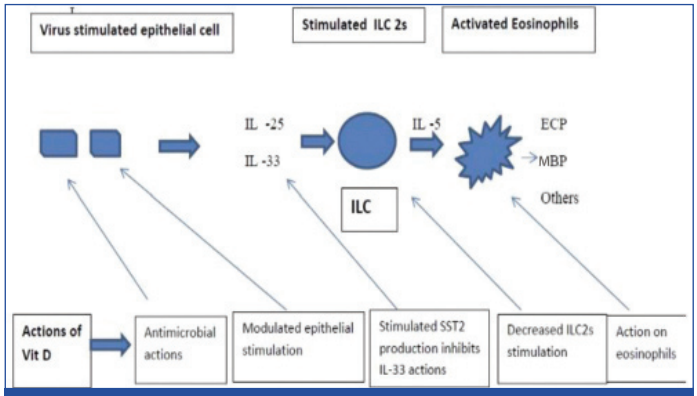
Vitamin D and Bronchial Asthma

Studies suggest that there is a relationship between serum Vitamin D levels and asthma-related symptoms probably via the immunomodulatory effects of Vitamin D. Airway inflammation is the key factor in asthma [9,10]. Vitamin D can protect against asthma morbidity by improvement of immunity in lung tissues, upregulation of antimicrobial proteins, overcoming steroid resistance by increasing

IL-10 and by anti-inflammatory and anti-proliferative effects on airway smooth muscle [11]. Vitamin D decreases inflammation, hyperplasia and cell cycling [12]. Vitamin D receptors polymorphisms are known to contribute to increased asthma susceptibility, providing a clue for the role of Vitamin D in asthma pathogenesis [13]. Vitamin D also acts on bronchial smooth muscle. Bronchial smooth muscle hyperplasia and hypertrophy contributes to airway narrowing [14]. Studies have shown that lower Vitamin D levels can cause bronchial smooth muscle proliferation, cytokine release and thus, airway remodelling [15,16]. Lower levels of Vitamin D in childhood are associated with increased bronchial hyperresponsiveness and later development of asthma [17-19]. Proposed mechanisms of asthma development in allergen induced asthma and non-allergic asthma are shown in [Table/Fig-3,4].



[Table/Fig-3]: Mechanism of allergen induced asthma and the role of Vitamin D.
Th:T helper; IgE: Immunoglobulin E; IL: Interleukin; T reg: T regulatory cells; LT: Leukotriene



[Table/Fig-4]: Mechanism of non-allergic asthma by epithelial injury and role of vitamin D.
ILC: Innate lymphoid cells, SST: Soluble suppression of tumorigenicity; IL: Interleukin; ECP: Eosinophilic cationic protein; MBP: Major basic protein

Vitamin D levels are significantly lower in asthmatics compared to non-asthmatics and is related to asthma control and severity [20]. A study on 100 adult asthmatics showed that Vitamin D levels were significantly lower in asthmatics compared to controls [12]. A study on Chinese asthmatic children showed that Vitamin D levels were lower than normal children, and lower levels had higher probability of asthmatic attacks [21]. A study [22] among Indian children found a definite relation between decrease in Vitamin D and severity of asthma, and improving Vitamin D status might prove important in decreasing exacerbations and better control of the disease. [Table/Fig-5] gives the in detail various studies of Vitamin D and its effects on bronchial asthma control [23-29].

Vitamin D and Pulmonary Functions

Black PN and Scragg R, observed that mean Forced Expiratory at 1 sec (FEV1) and Forced Vital Capacity (FVC) were lower in civilians with lower Vitamin D levels [30]. Choi CJ et al., also found a strong relationship between low 25(OH)D levels and poorer lung functions measured on spirometry [31]. A cross-sectional study on Chinese asthmatics showed 25(OH)D deficiency was very prevalent and was positively correlated with decreased lung functions, and remained significant even after adjusting for age, gender, Body Mass Index (BMI) and smoking [32]. Brumptonet BM et al., concluded that participants with low Vitamin D levels had higher decline in lung functions compared to those with high Vitamin D, and the association was stronger in non-smokers and non-inhaled corticosteroids users [33]. However, the Nord-Trøndelag Health Study (HUNT) study showed that low Vitamin D levels were associated with low FEV1/FVC only in men without allergic rhinitis [34]. Many studies in children showed similar results. In another study on asthmatic children showed Vitamin D levels were lower in asthmatics than controls and had direct and significant correlations with FEV1 [35]. An Iranian study showed the average serum Vitamin D levels were less than those in normal children and a positive correlation was found between Vitamin D levels and lung functions [36].

Somashekar AR, showed that Vitamin D was lower in asthmatics compared to controls and had a positive correlation with FEV1 [37]. Serum Vitamin D levels correlated with asthma severity, emergency department visits, and its deficiency is believed to contribute to asthma by increasing steroid resistance, airway hyperresponsiveness and airway remodelling. Various other studies have also showed positive correlations between Vitamin D and lung functions, asthma severity and control [38-42].

Vitamin D and Asthma Exacerbations

Viral infections are a common cause of exacerbations of asthma. The association between Vitamin D and upper respiratory tract infections were also found to be statistically significant [43]. The most common offending viruses are coronaviruses and rhinoviruses, which increase asthma exacerbation severity by inducing airway inflammation [44]. It has been observed that Vitamin D supplementation protected

Author	Study design	Study sample	Outcome measures	Findings
Urashima M et al., [23]	Randomised control trial on 217 children	School children with subgroup of clinically diagnosed asthma	Asthma exacerbations	Vitamin D supplement reduced the risk of severe asthmatic symptoms
Majak P et al., [24]	Randomised, double blind, parallel arm clinical trial six month study of Vitamin D3 in children	Newly diagnosed asthma	Asthma exacerbations	Children with Vitamin D supplement had lower incidence of asthma exacerbations
Yadav MK and Mittal K [25]	Randomised double blind placebo controlled trial on 100 children	Asthmatic children	Asthma exacerbations and number of emergency visits	Vitamin D had a role in bronchial asthma
Tachimato H et al., [26]	Treatment with Vitamin D in asthmatic children	Asthmatic children	Changes in childhood Asthma Control Test (ACT)	Asthma control was significantly improved in Vitamin D group, ACT score also improved.
Jensen ME et al., [27]	Active intervention with Vitamin D at baseline followed with daily dose	Asthmatic preschool children	Mean group change in Vitamin D from baseline to three months	Group difference in serum Vitamin D was not significant
Delinger LC et al., [28]	Cholecalciferol for 28 weeks or placebo	Adults with asthma	21-item Wisconsin upper respiratory symptom score	Vitamin D had no effect on average peak symptom score
Martineau AR et al., [29]	Six monthly oral dose of Vitamin D over one year	Adults with asthma	Asthma exacerbations and URTI	No significant association to first severe exacerbation or URTI

[Table/Fig-5]: Studies of Vitamin D and its effect on asthma morbidity [23-29]. URTI- Upper respiratory infection

against typical winter cold and influenza [45]. This protective role is presumably due to its ability to stimulate innate immunity and induce the expression of antimicrobial peptides such as defensins and cathelicidins.

Vitamin D levels in acute exacerbations of bronchial asthma were studied and it was observed that Vitamin D levels were lower in asthmatics group as compared to controls and lowest were seen in the severely exacerbated group [46]. Another author studied on adult asthmatics and showed that patients with 67.5% of bronchial asthma had less than normal Vitamin D levels [47]. They had lower pulmonary functions and increased number of exacerbations in the previous one year. There was a positive correlation between Vitamin D concentrations and asthma control. A study observed that Vitamin D levels were inversely related to the number of exacerbations in the last one year, inhaled corticosteroid score and Global Initiative for Asthma (GINA) asthma severity grades, and was directly related to FEV1% and FEV1/FVC ratio [48]. Confino-Cohen R et al., showed that low Vitamin D levels were not related to asthma prevalence but were related to asthma exacerbations, and there was an inverse association between proportion of asthmatics with exacerbations and Vitamin D levels [49]. Brehm JM et al., in Puerto-Rico also observed thatVitamin D levels were lower in asthmatics during exacerbations and there was a positive correlation between Vitamin D insufficiency and increased risk of severe exacerbations, lower FEV1/FVC ratio, that was independent of markers of disease severity or control [50]. Another study by Brehm JM et al., found that serum Vitamin D levels were inversely related to baseline FEV1 and bronchodilator responsiveness [51]. Higher Vitamin D levels were associated with lower odds of hospitalisation in the previous one year and are the strongest predictor of number of hospitalisations. A significant relationship between low serum Vitamin D and higher BMI, female sex, total Immunoglobulin E (IgE) levels was also observed. Another study found that Vitamin D insufficiency was associated with higher risk of severe asthma, increased hospital admissions, lower FEV1 and visits to emergency department [52].

Vitamin D and Steroids

Glucocorticoids induce the expression of Mitogen Activated Protein Kinases (MAPK-1) Mitogen Kinase Phosphatase (MKP-1), an inactivator of MAPK thereby producing an anti-inflammatory cell response. The molecular mechanisms of glucocorticoid resistance are complex and multifactorial. They include T regulatory cells, Interleukin-10 (IL-10), inflammatory gene expression and cytokines. Normal Vitamin D levels complement the action of inhaled steroids [53]. Steroid resistance and IL-17 responses are features of severe asthma and Vitamin D enhances the response to steroids in such individuals. Elevated serum Vitamin D levels were shown to have a positive correlation with glucocorticoid-induced MKP-1 expression in vitro. Hence, there is a synergistic effect of Vitamin D and inhaled corticosteroids on asthma outcomes [14]. Studies have shown corticosteroid use and worsening airflow limitations are associated with lower serum Vitamin D levels in patients with bronchial asthma [54]. Sutherland ER et al., have shown that Vitamin D supplementation could enhance glucocorticoid response in patients with asthma [55]. Gupta A et al., observed that Vitamin D levels were significantly lower in severe, therapy resistant asthma compared to moderate asthma and controls [56]. The daily dose of maintenance steroids were inversely related to Vitamin D levels. It was reported that in asthmatic children, Vitamin D levels were lower in children on inhaled corticosteroid therapy [57]. Recently, the authors did a study on Vitamin D levels in acute exacerbation on bronchial asthma, and it was observed that the prevalence of Vitamin D deficiency was 88.2% [58]. Patients with severe asthma and uncontrolled asthma had the lowest Vitamin D levels compared to controls. Vitamin D levels were lower in patients with severe exacerbation as compared to mild-moderate exacerbation. Thus, improving Vitamin D status might be effective in the prevention and treatment of exacerbations.

Vitamin D levels in Obese Asthma Patients

Studies have shown an association between reduced Vitamin D levels and obesity. Possible mechanisms include low dietary intake, reduced cutaneous synthesis, reduced intestinal absorption and sequestration in adipose tissue. There is also evidence that weight loss increases Vitamin D levels, which in turn provides additional protection from chronic diseases [59]. A study on bronchial asthma patients observed lower Vitamin D levels in severe and uncontrolled asthma [60]. It was also observed that lower Vitamin D levels were associated with poor asthma control, lower FEV1 levels and higher BMI. Shahin MY et al., observed an inverse relationship between Vitamin D and BMI [61]. Another study by Shebl RE et al., observed that Vitamin D levels were significantly lower in patients with bronchial asthma there was a significant negative correlation between Vitamin D levels and low BMI in asthmatic patients [62]. Menon B et al., studied the effect of Vitamin D supplementation on severity and control of asthma [63]. The study group received standard therapy along with oral Vitamin D (1000 IU) for eight weeks. It was observed that the mean Vitamin D in study group was 18.16±5.32ng/ml which improved to 27.16±7.61 ng/mL after supplementation as compared to the control group ($p<0.01$). Asthma Control Test score also improved after treatment. In conclusion there was highly significant improvement in asthma control and severity after supplementation with Vitamin D.

CONCLUSION(S)

Vitamin D deficiency is highly prevalent in patients with exacerbations of bronchial asthma. It is associated with increased number and severity of exacerbations, poorer asthma control, lower lung functions, and decreased quality of life. Studies have also shown that supplementation of Vitamin D has a significant positive effect in decreasing the severity and number of exacerbations of bronchial asthma, and this requires to be further confirmed by randomised studies in future.

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