



### Vitamin D and respiratory disorder

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#### ARTICLE INFO

##### Article type

Review article

##### Article history

Received: 2 Jan 2015

Revised: 20 Jan 2015

Accepted: 8 Feb 2015

##### Keywords

Asthma

Immunomodulation

Resistant asthma

Vitamin D

#### ABSTRACT

The active form of vitamin D is synthesized in some body organs following sun exposure and dietary intake. Vitamin D exhibits its major and critical effects not only through regulation of calcium and phosphate metabolism but also by influencing on respiratory and immune system. Serum concentrations of 25-hydroxyvitamin D below the optimum limit lead to vitamin D insufficiency or maybe deficiency. These inappropriate concentrations of vitamin D lead to different types of pulmonary diseases such as viral and bacterial respiratory infection, asthma, chronic obstructive pulmonary disease, and cancer. In this review we described the association between vitamin D deficiency and severe therapy resistant asthma. We also reviewed the underlying molecular mechanism of vitamin D deficiency in children with severe-therapy resistant asthma. Based on current information, future clinical trial are needed to study the role of vitamin D supplementation on different groups of patients with severe asthma including infants, children of school age, and ethnic minorities.

Please cite this paper as:

Hushmand M, Behmanesh F, Ahanchian H, Khalesi M, Ataei A. Vitamin D and respiratory disorder. Rev Clin Med. 2015;2(4):195-199.

#### Introduction

The association between steroid hormone vitamin D insufficiency and different diseases including cancers, autoimmune diseases, metabolic diseases, cardiovascular and respiratory abnormalities, has been studied in various articles (1-4). Asthma, allergy and respiratory infections draw the attention of researchers and showed an increasing trend due to huge number of related publication. Sunlight exposure will supply almost 90% of the human needed vitamin D and the rest is provided via appropriate food ingredients. 25-hydroxyvitamin D-1alpha-hydroxylase (1alpha-OHase) is known as a responsible enzyme for producing active form of vitamin D; 1,25-dihydroxvitamin D (1,25(OH)<sub>2</sub>D) from vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol) in the liver and kidney (5).

The active form of vitamin D is attached to vitamin D receptors (VDRs) and affects not only the calcium absorption, bone cell differentiation and activation, but also the immune responses (6). In this study, we tried to briefly review the association between serum concentration of vitamin D and pulmonary diseases such as allergy and asthma.

#### Literature review

##### *The active form of vitamin D*

Serum concentration of vitamin D prohormone (25(OH)D), which has a half-life of almost 3 weeks, is the most appropriate yardstick of vitamin D status. The concentrations of serum 25(OH)D as the vitamin D status index, lower than the optimum limit, which is still under consideration, is proposed

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as vitamin D deficiency or insufficiency, which might be diagnosed with no clinical presentation. According to Dietary Reference Intake (DRI), serum levels of 25(OH)D lower than 30 nmol/L lead to vitamin D deficiency (7).

The photosynthesis and bioavailability of 25(OH)D concentrations is under the influence of various factors such as race, vitamin D intake, sunlight exposure rate, obesity, age, some chronic diseases and physical activity (8). Both vitamin D2 and D3 are provided through sunlight exposure and transformation into 25(OH)D in the liver due to the function of 25-hydroxylases. Eventually, they convert to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] under the activity of 1 $\alpha$ -hydroxylase in the kidney. Although vitamin D deficiency or insufficiency can be determined based on 25(OH)D concentrations, it does not reveal the clinical and biochemical consequences, which are under the influence of vitamin D insufficiency time span, vitamin D receptor function, calcium intake, individual needs for calcium and individual variations (9).

Radioimmunoassay is the most prevalent technique in the assessment of 25(OH)D level, but it varies based on the method and different laboratories. Liquid chromatography–tandem mass spectrometry is also used to evaluate the total 25(OH)D (the level of both 25-hydroxylated D2 and D3).

Nutritional rickets and osteomalacia are significant presentations of vitamin D deficiency. Although vitamin D deficiency results in diseases, various skeletal and non-skeletal beneficial effects are proposed due to applying vitamin D supplementations. Increased bone mineral density, reduction of bone fracture rate, decreased mortality rate, reduced risk of colon and breast cancers, obesity, lower cardiovascular, metabolic, diabetes mellitus, multiple sclerosis, infection, mental illness, musculoskeletal pain, renal disease, allergy and asthma risks are other advantages of vitamin D (10).

### ***The association of vitamin D and asthma***

Based on some epidemiologic studies, maternal vitamin D situation during the prenatal period is negatively associated with childhood allergy and asthma. Vitamin D affects the immune system function and diminishes autoimmune diseases, but the relation between vitamin D levels and indices of allergy and asthma such as serum total and specific Immunoglobulin E (IgE) is not certainly indicated (11).

The efficacy of vitamin D in decreasing the prevalence of asthma is an attractive area of research. During the pregnancy, vitamin D is

influential on the lung development and the immune system. Thus, pre-birth cohort and clinical trials are the preferred types of studies (12). It is shown that increased administration of vitamin D during pregnancy can reduce the possibility of recurrent wheeze in the Northeastern United States (13).

Although asthma is manageable with low doses of steroids, almost 5-10% of patients are resistant to treatments and need intense healthcare (14). The involvement of vitamin D deficiency and insufficiency in some pulmonary diseases has been studied. Several studies revealed low vitamin D concentrations in children with various levels of asthma, which can lead to decreased lung function, increased exacerbation and drug application (15).

Brehm et al. in a cross-sectional study, showed that circulating concentrations of 25-hydroxyvitamin D had a statistically significant negative association with the total IgE and eosinophil counts in children of Costa Rica between the age 6-14. They proposed that vitamin D insufficiency could occur even in sun-replete regions (15). Another research group conducted a cross-sectional study revealed that vitamin D deficiency could attenuate the immune function and led to the respiratory infections, which were the main risk factors of asthma exacerbation (16).

Despite the effect of vitamin D on embryonic lung development, various sources can relate vitamin D concentration to different levels of asthma and allergy, which will be mentioned below. Due to the effect of Vitamin D on the immune system, it is suggested that T helper type 1, T helper type 2 and regulatory T cells are under the influence of vitamin D (17). In some articles, vitamin D is related to lung function, which can be proposed as another source to affect the asthma and allergy (18). Another study, used microarray technique, showed that vitamin D could affect the expression of responsible genes for morphogenesis, cell growth and airway remodeling in bronchial smooth muscle cells (19). Different regulations of vitamin D receptor responsible genes are suggested to be involved in occurrence of asthma phenotype in two studies (20,21).

### ***Severe-therapy-resistant asthma and serum vitamin D***

Limited number of studies has investigated the effect of different concentrations of vitamin D on children with therapy-resistant asthma (STRA). Table 1 summarized cross-sectional studies conducted on children to investigate the association of vitamin D with respiratory disorder. It has been indicated that significant reduced concentrations of vitamin D (<50 nmol/L) is more prevalent in

children with STRA than normal children or those with moderate asthma (15,16,22,27,29-34).

Gupta et al. suggested that reduced concentrations of vitamin D in children with STRA, was related with more intense manifestations such as lung function and inflammation (23). Based on their findings, the level of vitamin D has been significantly low in children with STRA, compared with the moderate asthmatic children.

Hypertrophy and hyperplasia have been detected in children with STRA, which lead to airway smooth muscle remodeling. According to in-vitro studies, calcitriol might be able to inhibit thrombin and platelet-derived growth factor that induced ASM cell proliferation through hyperphosphorylation of retinoblastoma protein and activation of checkpoint kinase 1 (Chk1). In these studies, vitamin D was suggested as an effective therapeutic agent in asthmatic patients acting through airway remodeling (24,25). Gupta et al. mentioned that airway smooth muscle hypertrophy was a structural impairment following embryonic vitamin D shortcoming which led to asthma. Moreover,

negative association has been identified between vitamin D level and airway smooth muscle mass remodeling (26). Reticular basement membrane thickness, epithelial shedding or airway smooth muscle cells proliferation are other risk factors of remodeling that have not shown any relation with vitamin D concentrations.

The relation between serum concentrations of vitamin D and other factors such as treatment rate with inhaled corticosteroid (ICS) and asthma exacerbation and control were studied in other investigations.

During 2009 to 2010, a group of researchers showed a significant negative relation between vitamin D concentration and asthma exacerbation. Based on their results, children with lower serum vitamin D levels had a higher rate of hospitalization or emergency department visit (odds ratio, 1.5; 95% CI, 1.1-1.9) (15,27). Other studies showed that a lower level of circulating vitamin D was related with significantly higher rate of corticosteroids administration. Based on in-vitro studies, vitamin D could increase the corticosteroids action and

**Table 1.** Studies relating vitamin D with respiratory disorder in children

Author Year Reference	Country	Patients number and age	Underlying disease	Association between vitamin D and risk of underlying disease
Erkkola 2009 (29)	Finland	1,669 children 5 years old	Asthma, allergic rhinitis in children	Inversely
Camargo 2010 (30)	New Zealand	929 newborns to 5 years old children	Asthma, wheezing	Inversely in wheezing, No association in asthma
Morales 2012 (31)	Spain	1,724 children 1-6 years old	Asthma, wheezing	No association
Pike 2012 (32)	UK	860 children 6-years old	Asthma, wheeze or atopy	No association
Brehm 2009 (15)	Costa Rica	616 children	Asthma, allergy	Inversely
Brehm 2010 (27)	African American	1,024 children	Asthma	Inversely
Brehm 2012 (33)	Puerto Rican	560 children	Asthma	Inversely
Chinellato 2011 (16)	Italy	75 children	Asthma	Inversely
Alyasin 2011 (34)	Iran	100 children	Asthma	Inversely

suppression of cell proliferation (15,28).

### **Molecular mechanism of vitamin D deficiency in patients with SRTA**

Based on investigations, vitamin D can induce the production of interleukin (IL)-10 by regulatory T cells, which regulates lymphocyte and monocyte responses to glucocorticoids. The underlying mechanism might be based on up-regulation of forkhead box P3 (FOXP3) in T regulatory cells. In this regard, applying vitamin D supplement might be useful in increasing the efficacy of dexamethasone in patients with steroid-resistant asthma (35).

Another mechanism of vitamin D might be due to decreasing the airway smooth mass through changing the expression of responsible genes. Vitamin D administration might be able to affect the cell cycle; decrease the airway smooth mass in S phase by diminishing the cells transition from G0/G1 to S phase through modulating phosphorylation of retinoblastoma and checkpoint kinase 1 proteins (25). In addition, regulating transcription of responsible genes in airway remodeling is another possible mechanism. The responsible function might be through the reduction of the mRNA and protein expression of metalloproteinase 9 (MMP9) and ADAM metalloproteinase domain 33 (ADAM33) genes and decreasing the ADAM33 protein expression (36).

The regulation effect of vitamin D on eosinophil migration increases the viability of isolated eosinophil (37). Another noticeable proposed role of vitamin D in patients with severe asthma is to diminish the proliferation and stimulation of transforming growth factor beta 1 (TGF- $\beta$ 1)-treated fibroblasts and to decrease the expression of extracellular matrix proteins (38).

Based on in-vitro experiments, 1,25(OH) $_2$ D $_3$  can inhibit nuclear factor-kappa B function and can eventually attenuate inflammatory responses following respiratory syncytial virus, which is known as a major pathogen respiratory tract (39).

### **Conclusion**

Although significant negative relation has been detected between serum vitamin D and allergy indicators, future double-blind and placebo-control clinical trials on various types of population are needed to establish the role of vitamin D.

### **Acknowledgement**

We would like to thank Clinical Research Development Unit of Ghaem Hospital for their assistant in this manuscript.

### **Conflict of Interest**

The authors declare no conflict of interest.

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