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Review Article

A review of Vitamin D effects on common respiratory diseases: Asthma, chronic obstructive pulmonary disease, and tuberculosis

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ABSTRACT

Despite the classic role of Vitamin D in skeletal health, new aspects of Vitamin D have been discovered in tissues and organs other than bones. Epidemiological and observational studies demonstrate a link between Vitamin D deficiency and risk of developing respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), and tuberculosis (TB). To review the literature, we searched the terms "Vitamin D" (using the set operator) and "asthma," "COPD" and "TB" in electronic databases, including PubMed/MEDLINE, Scopus, and Google Scholar until July 2015. Non-English articles or articles with unavailable full text were excluded. Both *in vivo* and *in vitro* studies were included. All the reviewed articles state that Vitamin D deficiency is very common among patients with respiratory diseases. The present data regarding Vitamin D and asthma is still controversial, but data about COPD and TB are more encouraging. The relevant studies have been conducted in different populations therefore it is not particularly possible to compare the data due to genetic variations. In order to point out a role for Vitamin D, large clinical trials with Vitamin D deficient subjects and sufficient Vitamin D supplementation are needed.

Keywords: Asthma; chronic obstructive pulmonary diseases; respiratory diseases; tuberculosis; Vitamin D

INTRODUCTION

Despite the classic role of Vitamin D in skeletal health, new aspects of Vitamin D have been discovered in tissues and organs other than bones. Epidemiological and observational studies demonstrate a link between Vitamin D deficiency and risk of developing respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), and tuberculosis (TB).

The topics "Vitamin D" (using the set operator) and "asthma," "COPDs" and "TB" were searched through the search engine in database such as PubMed/MEDLINE, Scopus, and Google Scholar until July 2015. Clinical trials and human studies only were included. Non-English articles or articles with unavailable full text were excluded. Both *in vivo* and *in vitro* studies were included. The search resulted in 46 articles about Vitamin D and asthma, 11 articles about Vitamin D and COPD, and 28 articles about Vitamin D and TB.

VITAMIN D AND RESPIRATORY DISEASES

Vitamin D has major effects in the respiratory system as it can affect pulmonary cell biology as well as its immunity. To support this idea, high expression of CYP27B1, which forms the active Vitamin D has been

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observed in the epithelial cells of lungs.[1] Studies also indicate a high significance between Vitamin D receptor (VDR) polymorphism and lower respiratory tract infections.[2] Epidemiological studies demonstrate that suboptimal level of Vitamin D is associated with a number of lung disease[3] including viral respiratory infections,[4] chronic rhinitis, rhinosinusitis,[5] COPD,[6] asthma,[7,8] and TB.[9]

ASTHMA

According to the Global Initiative for Asthma guidelines, asthma is a potentially serious chronic disease with symptoms such as wheezing, chest tightness, and cough. The interest to discover a relationship between asthma and Vitamin D was generated when observations indicated that Vitamin D deficiency and asthma have common risk factors including urban residence,[10,11] obesity,[12,13] and being African-American.[14,15] The beneficial effects of Vitamin D on asthma can be explained by several mechanisms. T-helper type 9 lymphocytes play an important role in the pathogenesis of asthma. Vitamin D can decrease inflammatory cytokines such as IL-9, IL-5, and IL-13 in these cells.[16] Steroid resistance is a major problem in the treatment of asthma. Vitamin D can overcome this resistance by generating IL-10-secreting regulatory T cells[17] and down-regulating the expression of FKN, a gene causing steroid resistance.[18] Even a combination of Vitamin D and dexamethasone were more effective in decreasing the inflammatory cytokines than dexamethasone alone.[16,19]

Vitamin D increases the expression of a peptide called cathelicidin which is a part of the innate immune system and an antimicrobial agent against *Mycobacterium tuberculosis* (MT), Gram-negative and Gram-positive bacteria, fungi, and viruses.[20] Maybe that is why Vitamin D deficiency can increase the risk of developing an infectious disease like influenza and influenza by itself can trigger asthma. Hyperplasia and excess proliferation of smooth muscle are important causes of chronic asthma and vascular endothelial growth factor, IL-6, and fibrinogen act as key factors in these processes. Vitamin D can down-regulate all of these factors[21] and give more time to the cells to repair DNA damage by preventing the cell from entering S phase.[22] Genes involved in Vitamin D pathways are associated with the pathogenesis of asthma, so Vitamin D and asthma may have a genomic-based relationship.[23] In animal studies reviewed, VDR-knockout mouse exhibited elevated levels of collagen deposition in airway tissue and pulmonary neutrophils, which increase hyperplasia in pulmonary tissues.[24] Vitamin D is also important in reducing airway inflammation, but this effect seems to be dependent on the baseline eosinophil levels.[25]

Several studies have investigated the relationship between maternal diet and risk of asthma.[26,27] It is also a fact that a maternal diet high in antioxidants and Vitamins D and E decreases the risk of childhood wheezing and asthma,[28-32] however one study did not find any evidence linking maternal diet and asthma in 5-year-old children except for apples and fish which have a reverse association with developing asthma.[33] An *in vitro* study by Miller *et al*. demonstrated that neonatal nasal airway epithelial which was exposed to the higher level of the maternal Vitamin D released higher IL-10 levels after exposure to tumor necrosis factor alpha (TNF-α) or house dust mite which can be important in developing asthma later in life.[34] One study by Chiu *et al*.[38] among 164 mother-infant pairs in Taiwan reported that there is a significant reverse relationship between maternal Vitamin D levels and specific IgE antibodies against allergens before age 2. On the other hand, treatment with $25(OH)_2D_3$ has been able to significantly decrease TNF-α production and frequency of CD16-positive monocytes.[35] As revealed by another study, Vitamin D supplementation could also decrease pro-inflammatory cytokine such as IL-17 and increase CD38 releasing B cells.[36] The largest prospective cohort measuring Vitamin D levels in pregnant women and following up the offspring for 20–25 years reported that not only high maternal Vitamin D has no effect on allergic airway disease or lung function, it even increases the risk for allergic disease in offspring.[37]

Children born to Vitamin D deficient mothers were more likely to develop eczema and asthma at age 4.[38] Another interesting study regarding the genomic effect of Vitamin D on asthma reported that single-nucleotide polymorphisms in the Vitamin D hydroxylase enzyme gene are associated with asthma diagnosis in children.[39] There is an ongoing clinical trial which examines the effect of Vitamin D supplementation among healthy toddlers which will report whether or not Vitamin D can decrease upper respiratory infections and asthma exacerbations among these children, and the most importantly it will establish the optimal dose of Vitamin D which should be used as a supplement.[40]

Observational data suggest that Vitamin D insufficiency is common among asthmatic children in the USA.[41] Among Qatari children, Vitamin D deficiency was a strong predictor of asthma[42] and was negatively associated with markers of asthma severity and exacerbation severity in children.[43,44] One study including 100 children stated that 60,000 IU Vitamin D per month could significantly reduce the severity of asthma and help patients better control asthma.[45]

Correlation between asthma and Vitamin D deficiency has also been investigated in adults. According to the clinical trial Vitamin D deficiency impairs lung function; increases airway hyperresponsiveness and can decrease the response to glucocorticoids,[46] but later on the larger clinical trial stated the otherwise. According to this study which included asthmatic patients with Vitamin D deficiency, supplementation with 100,000 IU at first and then 4000 IU/day of Vitamin D had no effect in improving glucocorticoid response or asthma exacerbation.[47] Data from the Third National Health and Nutrition Examinations Survey, conducting a cross-sectional study, including 14,091 participants during 6 years, revealed a significant relationship among Vitamin D, mean forced expiratory volume (FEV), and forced vital capacity.[48] Another clinical trial among asthmatic patients in Iran which followed the patients for 24 weeks and supplemented the intervention group with 100,000 IU bolus intramuscular (IM) Vitamin D and 50,000 IU weekly oral Vitamin D found that intervention group had a significantly enhanced FEV1.[49] Reactive airway dysfunction syndrome is a condition similar to asthma but does not respond to conventional asthma treatment. Varney *et al*. could successfully treat a patient who had this syndrome with high-dose Vitamin D.[50] Finally, one cross-sectional study including 15,212 individuals during a 2-year follow-up found no association between Vitamin D insufficiency and risk of asthma.[51] Of the latest clinical trials regarding Vitamin D and asthma, Martineau *et al*. conducted the clinical trial based on 3 mg Vitamin D_3 supplementation for over a year. Participants included 250 adults with asthma, and 82% of them had Vitamin D insufficiency. According to the results, Vitamin D supplementation had no effect on the asthma exacerbation or viral upper respiratory infections.[52]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD is a progressive disease, characterized by irreversible airflow destruction.[53,54] It's one of the most common lung diseases. The main etiologic processes which are related to lung damages in COPD are inflammation, oxidative stress, and pulmonary protease-antiprotease imbalance.[54-57] It is accepted that the inflammation of the small airways plays the principal role in the pathogenesis of the disease.[54] Although COPD is considered as an "adult" disease, researchers are focusing on finding early life factors contributing to the disease.[58,59] Like asthma, Vitamin D could be one of these early life factors, affecting early lung development. There are currently no epidemiological data to indicate an association between childhood Vitamin D deficiency and COPD, but *in vivo* and *in vitro* studies suggest a strong role for Vitamin D in lung development. For example experiments in the developing rat lung indicate that presence of Vitamin D in alveolar type II cells can increase surfactant synthesis and regulate epithelial-mesenchymal interactions.[60,61] There is also one study that suggests among culture cells; cigarette smoke exposure has a direct effect on Vitamin D pathways.[62] The mechanism of Vitamin D on the improvement of COPD is unclear. However, evidence proved that it can regulate the activity of immune cells,[3] improve the strength of airway muscles, and modulate inflammatory responses.[63] In COPD patients, there's a local down-regulation of Vitamin D signaling, which leads to an insufficient control of pro-inflammatory processes in the airways.[64]

According to recent findings, the prevalence of Vitamin D deficiency is between 33% and 77% among advanced COPD patients, which is significantly higher in COPD cases, compared with smokers without COPD.[6,65] Lower levels of Vitamin D in COPD may be explained with the reduction of cutaneous Vitamin D_3 production caused by smoking and limited sunlight exposure. Other mechanisms of Vitamin D deficiency could be reduced Vitamin D activation in liver and kidneys, increased Vitamin D sequestration in adipose tissue and decreased intestinal absorption.[55,66]

According to recent studies, there is a significant relationship between Vitamin D levels and lung function.[53,55] Research data indicated that serum 25(OH)D concentration is associated with the low FEV1 volume in patients with COPD.[67,68] In a prospective cohort study of 18,507 participants, the incidence risk of COPD was higher in the lower plasma 25(OH)D levels during the 20 years of follow-up.[69] In addition, recent findings demonstrated that serum level of 25(OH)D correlates with the severity of COPD[66] and affecting the severity of exacerbations.[70] However, it does not seem to be associated with the mortality rate in these patients.[71] Although baseline 25(OH)D levels are not predictive of acute COPD exacerbation.[72] Lehouck *et al*. reported that Vitamin D supplementation may reduce the COPD exacerbations in patients with severe deficiency.[73] Moreover, according to a pilot randomized trial, 2000 IU of daily Vitamin D for 6 weeks will increase serum 25(OH) D to a normal level in severe COPD patients.[74]

A recent cohort study of COPD cases demonstrated that serum 25(OH)D concentrations positively correlates with the maximal aerobic capacity

(VO_2 peak) and carbon monoxide transfer, so the low levels of Vitamin D could reduce the exercise capacity in these cases.[75] These findings are confirmed by the results of a randomized trial, which reported that Vitamin D supplementation could significantly improve the inspiratory muscle strength and exercise capacity, during rehabilitation in COPD patients.[76]

According to molecular and animal experiments, Banerjee and Panettieri described the effects of Vitamin D on airway smooth muscle cells in a review study. It's demonstrated that Vitamin D stimulates the airway smooth muscle cells to express VDR, which modulates the cell proliferation and inflammatory mediators' secretion. In addition, it can regulate the inflammation, contraction, and remodeling in other cell types.[77]

Studies indicate a high prevalence of osteoporosis and osteopenia among COPD patients.[78] Duckers *et al*. reported that COPD patients are more affected with osteoporosis and osteopenia compared with other smokers,[79] it confirms the results of other studies, which found a relationship between bone mineral density, severity of COPD, and Vitamin D levels.[80,81]

Although the longitudinal studies have proven the relationship between the serum Vitamin D status and COPD, recent data may impose doubt on the results. A recent study of 12,041 patients through 1993–2008 found a statistically significant inverse association between Vitamin D status and COPD prevalence, but Vitamin D status didn't correlate to the incident COPD.[82]

Moreover, there has been an attention toward the role of the Vitamin D-binding protein (VDBP; or Gc-globulin) in COPD disease.[83] Studies found a higher level of VDBP in COPD patients.[84] VDBP is a serum protein which involves in neutrophil chemotaxis and macrophage activation, which are believed to be important in COPD pathogenesis. The major amount of circulating Vitamin D is attached to VDBP, which has a positive effect on Vitamin D uptake.

Pro-inflammatory cytokines can affect the transcription of Gc-globulin, which may act as an acute phase reactant. It also interacts with neutrophil elastase, which plays the important part in COPD pathogenesis.[85] Other polymorphisms of the VDBP (rs7041 T allele) correlated with low Vitamin D levels and exhibited an increased risk for COPD.[6]

TUBERCULOSIS

Regardless of the success in the treatment of infectious diseases over the decades, TB remains one of the hardest infectious diseases to treat, due to an increasing rate of resistance to medication.[86] During the pre-antibiotic era, cod liver oil, a primary source of Vitamin D was used to treat TB, so the relationship between Vitamin D, and TB is not such a recent finding.[87]

People with TB infection are commonly involved with Vitamin D deficiency.[88] In fact, Vitamin D depletion could be a predictor of TB infections because of its essential functions in the immune system. 1,25-dihydroxy Vitamin D can effects MT by the production of the peptide called cathelicidin. Other than being an antiviral agent, cathelicidin has a direct antibacterial effect on MT.[89,90] The increased activation of toll-like receptor by Vitamin D also results in the production of defensin-2 and cathelicidin.[91] Vitamin D can induce autophagy of monocytes, as well as enhancing phagolysosome formation.[91,92] Furthermore, presence of Vitamin D is essential for interferon-gamma-mediated antimicrobial function of macrophages.[93] Another relevant role of Vitamin D in controlling TB could be its modulatory effect in T cell phenotype, balancing Th1, and Th2 responses.[94-96]

In attempt to find a role for Vitamin D in the treatment of TB, many studies have investigated the effect of Vitamin D supplementation on TB. The results of a meta-analysis including 531 participants reported that serum Vitamin D is reversely associated with risk of active TB.[97] One randomized clinical trial in Jakarta, supplementing TB patients with either 0.25 mg/day Vitamin D or placebo observed 100% sputum conversion in Vitamin D receiving comparing to 78.7% in placebo-receiving group.[98] However, another clinical trial including 365 patients with TB found no association between Vitamin D supplementation (100,000 IU in the start of TB therapy, 5 and 8 months later). According to the authors, these results could be due to the insufficient Vitamin D dose.[99] In a recent study, patients on supplementation with four doses of 2.5 mg Vitamin D displayed sputum clearance 1-week earlier than placebo, but this difference was not significant.[100] Another clinical trial comprising 259 TB patients received either 600,000 IU Vitamin D_3 IM or the matching placebo for 12 weeks. The results were favorable as Vitamin D group had the greater weight gain, smaller cavity size and decreased a number of pulmonary zones involved.[101] The most recent clinical trial with 2.5 mg Vitamin D at baseline and 2, 4, 6 weeks among TB patients indicate that this supplementation is unable to reduce time to sputum conversion.[102]

Interestingly among TB close contacts, a single-dose of 2.5 mg Vitamin D was able to enhance immunity response against MT.[103]

In additional, there is seasonality associated with TB incidence. In countries such as the UK, the incidence of TB is higher in spring, a season when serum Vitamin D level is low.[104-106] This seasonality has been observed in most of the countries including Europe,[107] South Africa,[108,109] and India.[110] One study by Strachan *et al*. among Asian immigrants in the UK indicated that a vegetarian diet, known to be low in Vitamin D, is a risk factor for development of TB, probably due to attenuated immune responses against MT.[111]

There is little information known about infants' immunity to TB regarding Vitamin D serum level, however one study reported 86% Vitamin D deficiency (below 20 nmol/ml) or insufficiency (below 75 nmol/ml) among children with active TB.[112]

Genetics are clearly relevant in the subject. Among Asians, those with the FokI FF genotype of VDR are the more susceptible to TB,[113] whereas the genotype of TaqI is a risk factor for developing TB among Gambian men.[114]

As a conclusion, administration of Vitamin D to patients with positive pulmonary TB who are taking anti-TB medication, benefited them by several means including shortened sputum conversion period, improved the inhibitory effect of treatment on monocyte count, inflammatory cytokines, chemokines, and Th1 cytokine response.[115]

DISCUSSION

Of the trials reviewed about asthma, the Third National Health and Nutrition Examinations Survey reported the beneficial effects of Vitamin D on asthma,[48] but in contrast the other two large sample studies; the Korea National Health and Nutrition Examination Survey and offspring cohort reported no such a thing.[37,51] Comparing the results of these two studies may not be wise because they are conducted on two different populations, with highly possible genetic differences and lifestyle. Among other studies, none of them reported the possible interaction of age on Vitamin D and asthma relationship and the most of the trials did not equally distribute the patients according to their sex or had the insufficient sample size.[116] It is also essential to measure Vitamin D serum levels at least 2 or 3 times during the study to reassure the serum level is as required.

Data on Vitamin D and COPD are more promising because in the majority of the studies, Vitamin D was associated with better lung function and could ameliorate COPD. Due to the high rate of bone problems associated with COPD, supplementing Vitamin D in this patients and correcting its deficiency seems vital. On the hand, recent data indicates there are many polymorphisms in the VDR gene, but the effect of VDR gene polymorphisms on the risk of respiratory infections in patients with COPD is largely unknown.[117,118] There is a hypothesis that COPD patients may have different genes predisposing them to Vitamin D deficiency and therefore, certain genes might be involved in the pathogenesis of COPD regarding Vitamin D. As a result these genetic variations could be the cause of discrepancies in Vitamin D and COPD relationship.[6]

Much of our knowledge about Vitamin D and TB centers mostly on Vitamin D's antibacterial effect regarding both innate and adaptive immune responses, however, other aspects of Vitamin D on TB, including its effect on latent TB is not as much investigated.[119] Of the reviewed articles, the majority found a beneficial role for Vitamin D in TB, but one clinical trial did not.[102] Further studies are needed to be initiated to assess the use of Vitamin D as an adjunctive therapy in TB infections. Most of the trials have been conducted using highly effective anti-TB therapy in which Vitamin D's effect is more likely to be modest, so larger trials with bolus doses of Vitamin D are needed to fully detect its role on TB. Treatment with Vitamin D is the most effective among deficient populations but in most of the trials the primary level of Vitamin D was not reported, or there was an overlap of Vitamin D's effect with genetic polymorphism resulting in different results among different populations. It should not be forgotten that using Vitamin D as a preventive agent could be even more important than a curative agent and therefore studies among healthy individuals who are at high risk for TB need to be designed to see if Vitamin D can help to prevent TB.

CONCLUSION AND FUTURE PERSPECTIVE

The relationship between Vitamin D and the respiratory system remains inconclusive. It is important to remember Vitamin D's effect beyond bone and calcium metabolism, but it would be immature to strictly point out a role for Vitamin D and accept it as a certain treatment for the mentioned diseases. Larger clinical trials and more comparable data are needed to put a closure on Vitamin D's association with different diseases. In either case, since there is a strong chance that this association really does exist and also Vitamin D deficiency is an epidemic all over the world, it is extremely important and recommended to prevent, diagnose and treat Vitamin D deficiency. Due to the great possibility of genetic involvement in Vitamin D's effect on respiratory disease and the high prevalence of Vitamin D deficiency in Iran, it is suggested to conduct clinical trials among the Iranian people and evaluate the efficacy of Vitamin D. The results may be different from those conducted in other populations. Health providers of the countries should take precautions to encourage people to spend more time in the sunlight and if necessary start fortifying food with Vitamin D. It also seems important to increase people's knowledge of how they can require Vitamin D and what the unhealthy consequences of Vitamin D deficiency are, because unlike usual vitamins which are believed to be obtained by a normal diet, Vitamin D's food source may not be that much abundant. Taken together, there are many studies that significantly showed the relation between Vitamin D deficiency and many diseases, however in some cases, the administration of Vitamin D could result in a better outcome, but for now and then there is limited number of thorough and conclusive studies showing the effect of Vitamin D supplementation on the outcome of diseases. If the role of Vitamin D on the diseases could be proved, a simple treatment of Vitamin D deficiency could solve many of the respiratory problems we are dealing with better outcome, fewer adverse effects, and less expensive treatment cost.

AUTHORS' CONTRIBUTION

Mohammad esmail-Hejazi: Data assembly and revision of the article. Faezeh.Modarresi-Ghazani: Literature search, writing the article. Taher Entezari-Maleki: Article revision, grammar revision.

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