Review

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Relationship of Vitamin D and Respiratory Diseases

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ABSTRACT

Researchers in recent years have shown that vitamin D deficiency is closely linked to respiratory diseases, in addition to bone calcium and phosphorus regulation. In depth study of vitamin D, vitamin D receptor helps to further elucidate the pathogenesis of certain respiratory diseases. Vitamin D supplementation plays an important role in the prevention of lung cancer, pulmonary fibrosis, pulmonary edema, lung injury, and so on. In this review, we summarized the research progress of the relationship of vitamin D with certain respiratory diseases mentioned above, so as to help to bring new ways of prevention and treatment of respiratory diseases breakthrough.

KEYWORDS: Vitamin D; Vitamin D receptor; Respiratory diseases.

ABBREVIATIONS: FIRS: Forum of International Respiratory Societies; COPD: Chronic Obstructive Pulmonary Disease; APE: Acute Pulmonary Edema; ARDS: Acute Respiratory Distress Syndrome; VDR: Vitamin D Receptor.

INTRODUCTION

Vitamin D is a fat-soluble vitamin, sterol derivatives. Recent investigations suggested that vitamin D plays its roles through its nuclear hormone receptors-vitamin D receptor (VDR), the steroid hormone nuclear receptor. VDR mediates most known functions of vitamin D, and is widely distributed in various tissues and cells in the body, such as skin, intestine, lung, kidney and other organs. Mounting evidence indicates that vitamin D and VDR play key roles in the pathogenesis of human diseases. However, how the vitamin D/VDR signaling is involved in human tissues and cells related to lung diseases remains largely unknown. In this review, we will summarize the recent research progress in the roles of vitamin D/VDR signaling in certain respiratory diseases associated with vitamin D deficiency.

VITAMIN D AND VITAMIN D RECEPTOR

Vitamin D is produced in skin upon exposure to ultraviolet radiation from the sun or from limited dietary sources such as fish, irradiated mushrooms and fortified foods such as milk and orange juice. Researchers reported the first determination of the structure of VDR in 2000. Since then more and more researches focus on developing new VDR ligands as therapeutic agents. The most biologically active metabolite is 1,25-dihydroxyvitamin D_3 (1,25(OH)_2D_3), which depends on the activity of 1α-hydroxylase and 25-hydroxylase. However, the expression of VDR is to determine whether the activity of vitamin D can play a role in human tissues and cells. VDR belongs to the family of trans-acting transcriptional regulatory factors and shows sequence similarity to the steroid and thyroid hormone receptors. It is mainly involved in mineral metabolism and a variety of other metabolic pathways, mediates the cellular effects of vitamin D and interacts with other cell signaling pathways that influence cancer development, and...
so on. Vitamin D deficiency is caused by inadequate nutritional intake of vitamin D coupled with inadequate exposure. Alternative splicing results in multiple transcript variants encoding different proteins. Numerous studies investigated the associations of VDR polymorphisms with various types of cancer, such as lung cancer, intestine tumor and other cancers, as independent contributors or in combination with vitamin D concentration. Therefore, the VDR is a key player in dynamic balance of minerals in the body, cell growth and immune responses. It is not surprising that altered signaling and functions of VDR has a close link in human diseases with vitamin D deficiency.

VITAMIN D ANALOGS

Vitamin D analogs provide a convenient pathway in further studying vitamin D, such as calcitriol, doxercalciferol, and paricalcitol. They are used to activate the vitamin D signaling pathways and VDR activators supplementation is used to enhance the VDR activation and is associated with better survival in certain human diseases. Mounting evidence indicate that lung diseases, inflammatory bowel disease, skin disorders, chronic kidney diseases and other diseases have been treated with vitamin D analogs and VDR modulators. Epidemiological evidence indicate that the use of VDR activators is an independent predictor of a lower risk of death from cardiovascular disease in patient with chronic kidney disease.

VITAMIN D AND RESPIRATORY DISEASES

Vitamin D deficiency appears to be frequent among patients with lung diseases, including asthma, chronic obstructive pulmonary disease, lung cancer etc. The patients with the above diseases often have low vitamin D serum levels. Vitamin D appears to impact on the function of inflammatory and structural cells, including dendritic cells, lymphocytes, monocytes and epithelia cells. There is an increasing number of experiments identified that vitamin D, VDR and vitamin D binding proteins are closely related with lung diseases.

Vitamin D and Lung Cancer

Lung cancer is the leading cancer in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths. The mortality burden for lung cancer among females accounts for 11% of the total female cancer deaths. In recent years, the relationship between vitamin D and prevention of lung cancer from the published reports are still conflicting. Cheng et al investigated whether estimated vitamin D intake was associated with lung cancer risk and whether the effect modification by vitamin A existed among current/former heavy smokers and workers with occupational exposure to asbestos. Their observation suggested that vitamin A assists vitamin D in preventing lung cancer among smokers. Moreover, the study suggests that there was a strongly linked relationship between taking total vitamin D 400 IU versus <400 IU/day and a lower risk of total lung cancer.

Current research has implicated that vitamin D deficiency is a critical factor in the pathology of various kinds of cancers besides lung cancer. The relationship between the VDR polymorphisms and the susceptibility to lung cancer remains unclear. Many epidemiological studies suggest that the VDR BsmI polymorphism seems to be negatively associated with the lung cancer risk. Fu et al found that the VDR BsmI and TaqI polymorphism played protective roles in the development of lung cancer, especially among the smokers. Zhong et al reported that B allele bb genotype allele and TT genotype were associated with lung cancer risk in overall populations by using meta-analysis method. The association of VDR Apal polymorphism with the lung cancer risk needs to be investigated.

Borkowski et al utilized a library of oligonucleotide inhibitors to microRNAs, a class of post-transcriptional gene regulators, to identify novel synthetic lethal interactions between miRNA inhibition and molecular mechanisms in non-small cell lung cancer. They found that miR-92a and miR-1226 inhibitors cause sequence-specific down-regulation of the miR-17~92 polycistron, and this down-regulation was toxic only in the context of p53 loss. They reported that VDR agonists may be positively efficacious in p53-negative lung cancer patients.

Vitamin D and Tuberculosis

As described in recent reports of the Forum of International Respiratory Societies (FIRS), tuberculosis is one of the leading causes of death in the world. It is estimated that one third of the world’s population were infected with tuberculosis, but only 10% of them have developed into disease. A prospective cohort study was conducted to assess the relationship between serum baseline vitamin D status and the incidence of tuberculosis among 572 contacts of 89 pulmonary tuberculosis patients in Castellon, Spain. Arnedo et al estimated that the relationship between serum vitamin D status and tuberculosis infection conversion, measured by the tuberculin skin test and an interferon-gamma release assay, the Quantiferon-TB Gold In-Tube test, in the contacts of pulmonary tuberculosis patients in Castellon in a prospective cohort study. These epidemiological studies, taken together, suggest that sufficient vitamin D level could be a protective factor of tuberculosis infection conversion.

Vitamin D performs its actions through the VDR, which acts as a transcriptional factor. Sinaga et al utilized matched case-control study and PCR-RFLT to prove that there was no association between FokI polymorphism of VDR gene with host susceptibility to pulmonary tuberculosis, however, the BsmI polymorphism of VDR gene contributes to reducing the risk of pulmonary tuberculosis. Ampel meta-analysis investigated that Apal polymorphism of VDR gene is significantly associated with a decreases risk of tuberculosis.
Vitamin D and Asthma

Asthma is a disorder characterized by various and recurring symptoms of airflow obstruction and bronchial hyper-responsiveness in the setting of inflammation. Recent epidemiologic data suggested that there was an association between vitamin D deficiency and asthma, and noted that asthma prevalence is highest in countries furthest from equator. Vitamin D supplementation protects against childhood asthma during the period of promoting perinatal lung maturation as well as surfactant synthesis by type II alveolar cells. Additionally, there is a association between serum vitamin D levels and steroid requirement in pediatric patients, but not adults. In pre-school children with severe intermittent wheezing, a 25(OH)D level below 20 nmol/l was associated with a higher rate of exacerbations requiring oral corticosteroids. Brehm et al examined the relationship between baseline vitamin D levels and the odds of any hospitalization or emergency department visit over the 4 years of the trial by using the multivariable models. They reported that in the population of North American children with mild-to-moderate persistent asthma or severe exacerbation over a 4-year period are usually vitamin D insufficiency. Healthy children are likely to be more physically active, than children with severe asthma. Tian et al indicated that 1,25(OH)2D3 play a important role in reducing on airway inflammation, airway hyper-responsiveness and airway remodeling by partially inhibiting chemokine production during airway inflammation, and 1,25(OH)2D3 synergises with hormone therapy. They examined IgE, eotaxinm and IL-8 expression levels in the vitamin D group, which are significantly lower than those in the asthma group.

Ample evidence found 1,25(OH)2D3 and VDR are essential to regulate the innate immunity. Vitamin D may act on the immune system to dampen inappropriate inflammatory response in the airway while also promoting tolerance and antimicrobial defense mechanisms that collectively maintain respiratory health. Calcitriol is an important determinant of muscle cell proliferation and differentiation, as well as inhibition of apoptosis. The immunoregulatory properties of vitamin D have been demonstrated in studies showing that vitamin D deficiency is associated with poor immune function and increases disease susceptibility. ChIP analysis using 1,25(OH)2D3 treated human lung epithelial cells showed C/EBPα and VDR binding to cAMP promoter. These findings suggest potential candidates for the development of modulators of innate immune responses for adjunct therapy in the treatment of asthma. Moreover, available evidence indicated that the impact of TaqI, BsmI, and FokI VDR polymorphisms contribute to asthma disease susceptibility by using a meta-analysis approach.

Vitamin D and Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a significant public health burden. It is a chronic inflammatory airway disease characterized by progressive destruction of the lung emphysema and/or chronic inflammation of the small airways leading to hyperinflation and fixed airflow obstruction. The date from the ample epidemiological studies suggested that there is a closely association between vitamin D and lung function. Recently, Rafiq et al performed a randomized, multicenter, doubled-blind, placebo-controlled intervention study, which enrolled 240 chronic obstructive pulmonary disease patients aged 40 years and older with vitamin D deficiency. Participants were assessed by undergoing spirometry, total lung capacity and maximal respiratory mouth pressure. They found that vitamin D played a protective role against exacerbations in deficient patients.

Vitamin D and Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) accounts for one-quarter of cases of acute respiratory failure in intensive care units. The disruption of the vascular endothelial barrier is a major factor in the protein-rich edema formation and inflammatory cell infiltration that characterize diseases such as acute respiratory distress syndrome. Recent studies have shown that vascular endothelial protein tyrosine phosphatase is a HIF2α target. Their observation suggested that activation of transcription factor HIF2α/vascular endothelial protein tyrosine phosphatase signaling via polyhydroxylase domain 2 inhibition plays a potential role in preventing the formation of leaky vessels and edema in inflammatory disease such as acute respiratory distress syndrome. Several studies have reported that calcitriol suppresses inflammation. Zhang et al found that pretreatment with calcitriol significantly inhibited the activation of NF-κB and RhoA/Rho kinase pathways. Moreover, treatment of calcitriol also improved lung histopathologic changes, reduced inflammation and lung edema.

Vitamin D and Acute Pulmonary Edema

Acute pulmonary edema (APE), the interstitial or alveolar pulmonary edema syndrome, refers to hypoxemia and diffuse infiltration of neutrophils into the alveolar space. The clinical features on which the acute pulmonary edema episode occurred were represented by severe difficulty breathing or coughing up pink foamy sputum. Acute pulmonary edema represents a major emergency that require immediate admission to hospital and rapid treatment in the emergency department concurrent with the identification of the triggering and precipitating factors. More and more people focus on the treatment of acute pulmonary edema.

Available evidence indicated that epithelial sodium channel (ENaC) was critical in the acute pulmonary edema. Ample evidence suggests that ENaC, especially for the α-ENaC plays a critical role in alveolar fluid clearance. In previous studies, netrin-1 has been shown that it is a newly found anti-inflammatory factor that works by activating the adenosine 2B re-
ceptron. Meanwhile, activated adenosine 2B receptor has potential to enhance ENaC-dependent alveolar fluid clearance. He et al established acute lung injury model by intratracheal instillation of lipopolysaccharide in C57BL/6J mice, followed by netrin-1 with or without pretreatment with PSB1115, via the caudal vein. They found that netrin-1 expression was significantly decreased during acute lung injury in vivo. Moreover, netrin-1 increases the expressions of α-, β, and γ-ENaC, which were prevented by PSB1115. These results, taken together, suggest that netrin-1 dampens pulmonary inflammation and increases ENaC-mediated alveolar fluid clearance to alleviate pulmonary edema in lipopolysaccharide-induced acute lung injury by enhancing cAMP levels through the activation of adenosine 2B receptor.

Jiang et al established acute pulmonary edema model by exposing to H2S, in parallel, A549 cells were treated with NaHS to establish cell model. They indicated that dexamethasone, a potent anti-inflammatory agent, significantly attenuated H2S-induced lung histopathological changes and alveolar fluid clearance decrement. However, mifepristone, the glucocorticoid, can obviously slow the effects of dexamethasone. Moreover, dexamethasone markedly attenuated H2S-mediated α-ENaC down-regulation, and similarly, the process can be partially retarded by mifepristone. Dexamethasone obviously prevented H2S-mediated acute pulmonary edema, and α-ENaC might be a potential therapeutic target for acute pulmonary edema induced by H2S.

Vitamin D and Acute Lung Injury

Epidemiological studies have emerged for the association between vitamin D levels at the onset of critical illness and the development of acute lung injury. Studies have investigated the effect of VDR deletion on acute lung injury using a lipopolysaccharide-induced sepsis model. Kong et al found that vitamin D blocked lipopolysaccharide-induced Ang-2 expression by blocking nuclear factor-kB activation in human pulmonary artery endothelial cells. Moreover, they provide evidence that the vitamin D-VDR signaling prevents lung injury by blocking the angiopoietin-2-Tie-2-myosin light chain kinase cascade and the rennin-angiotensin.

Available evidence suggested that the chemokine interleukin-8 is an important factor in acute lung injury. Takano et al determined its effects of 1,25(OH)2D3 in a hamster model where acute lung injury was induce by lipopolysaccharide inhalation. They found 1,25(OH)2D3 inhibited neutrophil recruitment in the lung by approximately 40% without increasing plasma calcium concentration, while it did not inhibit monocyte recruitment. These results, taken together, suggested that 1,25(OH)2D3 analogs may be suitable as novel anti-inflammatory agents for acute lung injury.

CONCLUSION

Till now, there are no universal guidelines for vitamin D insufficiency in the lung diseases. This review summarizes the knowledge of vitamin D, the molecular and cellular mechanism of action and the available data on the relationship between lung disease and vitamin D status. More information on the role of vitamin D in the lung diseases is required to provide new ideas and perspectives to treat relative lung diseases.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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