Vitamin D deficiency and chronic lung disease

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Vitamin D deficiency is increasingly being recognized as a prevalent problem in the general population. Patients with chronic lung diseases such as asthma, cystic fibrosis, chronic obstructive lung disease and interstitial pneumonia appear to be at increased risk for vitamin D deficiency for reasons that are not clear.

Several studies indicate that vitamin D possesses a range of anti-inflammatory properties and may be involved in processes other than the previously believed functions of calcium and phosphate homeostasis. Various cytokines, cellular elements, oxidative stress and protease/antiprotease levels appear to affect lung fibroproliferation, remodelling and function, which may be influenced by vitamin D levels. Chronic lung diseases such as asthma and chronic obstructive lung disease have also been linked to vitamin D on a genetic basis. This immune and genetic influence of vitamin D may influence the pathogenesis of chronic lung diseases. A recent observational study notes a significant association between vitamin D deficiency and decreased pulmonary function tests in a large ambulatory population.

The present review will examine the current literature regarding vitamin D deficiency, its prevalence in patients with chronic lung disease, vitamin D anti-inflammatory properties and the role of vitamin D in pulmonary function.

Key Words: *Chronic lung disease; Chronic obstructive pulmonary disease; Pulmonary function testing; Third National Health and Nutrition Examination Survey; Vitamin D deficiency*

La carence en vitamine D et la maladie pulmonaire chronique

La carence en vitamine D est de plus en plus reconnue comme un problème prévalent au sein de la population. Les patients atteints d'une maladie pulmonaire chronique comme l'asthme, la fibrose kystique, la maladie pulmonaire obstructive chronique et la pneumonie interstitielle semblent être plus vulnérables à la carence en vitamine D, pour des raisons qui ne sont pas claires.

Selon plusieurs études, la vitamine D est pourvue d'une série de propriétés anti-inflammatoires et pourrait participer à d'autres processus en plus des fonctions d'homéostasie du calcium et du phosphate. Diverses cytokines, des éléments cellulaires, le stress oxydatif et les taux de protéase et d'antiprotéase semblent avoir une incidence sur la fibropolifération, le remodelage et la fonction pulmonaires, sur lesquels la vitamine D pourrait influer. Des maladies pulmonaires chroniques, comme l'asthme et la maladie pulmonaire obstructive chronique, sont également liées à la vitamine D sur une base génétique. Cette influence immune et génétique de la vitamine D pourrait agir sur la pathogenèse des maladies pulmonaires chroniques. Une récente étude d'observation indique une association importante entre la carence en vitamine D et une diminution des résultats aux explorations fonctionnelles respiratoires au sein d'une vaste population ambulatoire.

La présente analyse contient un examen des publications courantes au sujet de la carence en vitamine D, de sa prévalence chez les patients atteints d'une maladie pulmonaire chronique, des propriétés anti-inflammatoires de la vitamine D et du rôle de la vitamine D dans la fonction pulmonaire.

Lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), asthma and the idiopathic interstitial pneumonias are common chronic diseases in the United States and worldwide. They are associated with high morbidity and mortality, along with significant cost and use of health care systems (1).

The present article will review the literature regarding the role and prevalence of vitamin D deficiency in patients with chronic lung disease, along with potential mechanisms for the involvement of vitamin D in lung disease.

CHRONIC LUNG DISEASE AND INFLAMMATION

In the United States, over 35 million people live with COPD (1) along with another 30 million people with asthma (2). Other chronic lung diseases such as CF and idiopathic pulmonary fibrosis are much less common, but are associated with significant morbidity and mortality.

Many of the chronic lung diseases have an inflammatory component related to their underlying dysfunction. This pathophysiology and altered immune response will be reviewed at this point.

COPD

Alpha-1 antitrypsin deficiency and exposure to cigarette smoke are known to significantly increase the risk for the development of COPD (3,4). The exact pathogenesis has yet to be discovered; however, numerous cellular elements have demonstrated involvement in the pathophysiology of COPD. These include macrophages, neutrophils and cytokines such as interleukin (IL)-4, IL-5 and IL-13, along with interferon-gamma (4-6).

Patients with COPD demonstrate markedly increased baseline levels of proinflammatory cytokines (7). Lymphocytes, specifically CD8 T lymphocytes, are present in increased numbers in those with symptomatic chronic obstructive lung disease

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compared with those without symptoms (8). Weak associations have also been found between increased CD8 T lymphocytes and decreased forced expiratory volume in 1 s (FEV_1) in patients with COPD (9). These observations, however, have not been confirmed as a primary event or a secondary response (4,7).

The alveolar wall destruction and loss of elastic recoil that occur in COPD are believed to be the result of chronic inflammation and imbalance of antioxidants (5,10). Oxidative stress appears to be increased in patients with COPD compared with healthy subjects and those with comparable smoking histories but no evidence of obstructive lung disease. This oxidative stress causes a protease/antiprotease imbalance and is believed to be a contributing factor toward the pathogenesis of COPD (10).

Asthma

Airway inflammation is one of the hallmark features of asthma. Dysregulated T helper cells and an abnormal inflammatory response, including increased levels of IL-4, IL-5, IL-9 and IL-13, may be responsible (6). This response results in infiltration of eosinophils, lymphocytes and macrophages within the airways (11). Inflammation that occurs repeatedly over a long time can be associated with fibrous deposition and smooth muscle hypertrophy (11). Increased degradation of elastin and increased expression of proteases have also been discovered in patients with asthma (6), implicating that the disease may not be completely reversible.

Idiopathic interstitial pneumonia

Idiopathic interstitial pneumonias are believed to occur as a result of an aberrant host response to inflammation and epithelial cell injury. This response often results in significant fibroproliferation. There are many theories as to the exact etiology of the inflammation, but concepts such as oxidative stress, macrophage dysfunction and various cytokines have all been suggested (12).

CF

CF occurs as a result of specific gene mutations leading to an abnormal CF transmembrane conductance regulator. A recent review (13) notes that continued pulmonary inflammation, even in the absence of infection, appears to play a large part in the continued disease process. Treatment with certain anti-inflammatory medications may help downregulate the immune response and improve pulmonary function test results (14).

Many of these previously mentioned diseases have an underlying component of inflammation or immune dysfunction related to their pathophysiology. Vitamin D deficiency may have some role in this altered immune response process.

VITAMIN D METABOLISM AND DEFICIENCY

Vitamin D is an essential element to human diets and is acquired by one of two methods. Vitamin D can be obtained from dietary supplementation or synthesized in human skin following exposure to sunlight. Dietary sources include supplemented dairy products, fish oil, fish liver and eggs (15).

Vitamin D deficiency is often the result of three major causes: malabsorption, inadequate sun exposure or inadequate nutrition. A low serum 25-hydroxyvitamin D level defines vitamin D deficiency (15); however, there has been no formal agreement on acceptable levels of vitamin D in the body. The majority of experts accept that serum 25-hydroxyvitamin D_3 levels less than 10 µg/L (25 nmol/L) place adult patients at high risk for osteomalacia (or rickets in children). There are no consensus guidelines available from professional endocrinology or vitamin D societies, but many have been recommending that a desirable vitamin D concentration should be above 30 µg/L (75 nmol/L) (16).

Vitamin D deficiency appears to be an under-recognized and underdiagnosed disorder in the general population. In 1998, a study (17) performed on an inpatient medical population demonstrated that vitamin D deficiency is quite common. Depending on the levels used to define vitamin D deficiency, 57% to 93% of the general inpatient population was defined as deficient. Vitamin D levels in these patients were believed to be variable for a number of reasons, including dietary intake, physical activity and sun exposure. Other risk factors for variable vitamin D levels include sex, age, socioeconomic status and tobacco abuse (15).

VITAMIN D EFFECTS BEYOND BONE METABOLISM

Vitamin D and parathyroid hormone are the regulators of calcium and phosphate homeostasis in the human body. Vitamin D and its metabolites are known to target receptors located on the kidneys, intestines and bone. Calcitriol increases intestinal calcium absorption, osteoblastic bone formation and osteoclastic recruitment leading to bone resorption (18). More recent research has revealed new sites of action that may force the re-examination of vitamin D and its role in human physiology. Vitamin D receptors (VDRs) have been found in organs not typically believed to be involved with bone metabolism, including the pancreas, gonads, liver, heart, brain and breast, as well as the hematopoietic and immune systems (15).

Calcitriol has demonstrated an ability to encourage differentiation of normal cell types (such as lymphocytes, hematopoietic cells, osteoblasts and osteoclasts) and may produce significant effects on other aspects of the immune system (15). Further studies support the concept that vitamin D has the ability to affect immune function, along with its potential use as a treatment modality in a variety of diseases. Vitamin D analogues, such as calcipotriene, are commonly used in the treatment of psoriasis. Both in vitro and in vivo studies have been able to demonstrate immunomodulatory effects of vitamin D on the skin (19). Experimentally, vitamin D has been shown to play a role in the prevention of the development of certain autoimmune diseases such as ulcerative colitis and Crohn's disease (20).

VITAMIN D AND LUNG DISEASE

The effect that 25-hydroxyvitamin D levels in patients with chronic lung disease may have on pulmonary function has not been extensively studied. However, there are a number of proposed mechanisms and potential connections between vitamin D and lung disease.

Proposed mechanisms

As mentioned previously, proposed mechanisms of oxidative stress, protease/antiprotease imbalance and tissue damage/repair are all processes that may play a role in the pathogenesis of

chronic lung diseases such as COPD and CF (13,21). Matrix metalloproteinases (MMPs) are enzymes implicated in inflammation and cellular movement within the lung. These MMPs have been studied regarding their involvement in the remodelling and inflammation process of COPD (22), along with inhibition of smooth muscle airway remodelling in asthma (23). Increased MMP levels have been found in the sputum of patients with CF (24). Timms et al (25) demonstrated that vitamin D levels were inversely related to the level of circulating MMP (MMP-9) in 171 healthy adults. Noting this relationship, they supplemented a subset of their study population with vitamin D and found a significant reduction in the MMP-9 levels. These studies help provide a possible mechanism to support the connection between vitamin D deficiency and lung inflammation/degradation.

Prevalence of vitamin D deficiency in chronic lung disease

Vitamin D deficiency has been established as exceedingly prevalent in many of chronic lung disease populations. Fifty-nine per cent of patients with diffuse parenchymal lung diseases undergoing evaluation for lung transplant were found to have decreased vitamin D levels (26). COPD patients without any glucocorticoid use had significantly decreased 25-hydroxyvitamin D levels when compared with age-matched controls (27). Children with a diagnosis of wheezy bronchitis had more than two-and-a-half times the incidence of rickets than the age-matched controls. Also noted was a 10 times higher incidence of wheezy bronchitis when severe rickets was present (28). Limited studies (29,30) in patients with chronic lung disease suggest that bone mineral density is correlated with lung function, whereas another study (31) was unable to confirm this.

Pulmonary function and vitamin D deficiency

The best evidence to date regarding a connection between vitamin D deficiency and lung function is the Third National Health and Nutrition Examination Survey (NHANES III). NHANES III was an observational, cross-sectional survey that analyzed data collected from more than 14,000 noninstitutionalized adults older than 20 years of age. Data such as age, sex, height, weight, smoking history, vitamin A, C, D and E supplementation, pulmonary function tests and dietary intake, including antioxidants, were collected.

Analysis of the data revealed a number of interesting findings, including a significant association between vitamin D (25-hydroxyvitamin D) levels and pulmonary function tests, specifically FEV_1 and forced vital capacity (FVC) (32). Adjusting for variables such as age, sex, smoking history, height, ethnicity, history of asthma/bronchitis and body mass index demonstrated a mean difference of FEV_1 by 126 mL and FVC by 172 mL ($P<0.0001$ for both) between the lowest and highest quintile of vitamin D levels (32).

Further adjustments for leisure time activity, antioxidant intake and dietary intake maintained a significant difference between FEV_1 by 106 mL and FVC by 142 mL ($P<0.0001$ for both) for the lowest and highest quintile of vitamin D levels. A potential confounding factor in this analysis was believed to be a lack of physical activity in some subjects. However, excluding these individuals from the analysis still demonstrated a difference in FEV_1 of 127 mL between the lowest and highest quintile of vitamin D levels. There was, however, no difference in the FEV_1/FVC ratio between the highest and lowest quintiles of vitamin D levels (32). This finding suggests that the pulmonary function changes observed are not the result of worsening obstructive lung disease.

Other observations that did not reach statistical significance include an association between FEV_1 and 25-hydroxyvitamin D levels in people with a smoking history, along with those older than 60 years of age. Also, in analyzing the highest and lowest quintiles of 25-hydroxyvitamin D levels, the difference in FEV_1 was greatest in subjects with chronic bronchitis (248 mL) and emphysema (344 mL). However, the interaction between emphysema and chronic bronchitis with regard to vitamin D levels was not significant (32).

COPD and vitamin D

Further investigations into the role of vitamin D in chronic lung disease include its involvement in COPD. This includes examination of the role of vitamin D binding proteins (VDBPs), which are crucial for the transport and regulation of vitamin D metabolites (33). Kueppers et al (34) initially described the protective effect (RR 0.2) from developing COPD by the presence of the Gc2 allele. Horne et al (35) examined VDBPs in COPD and confirmed that the presence of a homozygous Gc2 allele offered protection (RR 0.8) from developing COPD. They also discovered that the presence of homozygous 1F allele offered an increased risk (RR 4.8) for the development of COPD. Ishii et al (36) were able to confirm that patients with COPD demonstrated an increased incidence of the homozygous 1F allele. Further study by Schellenberg et al (37) confirmed that VDBP (specifically the Gc2 allele) offers protection from the development of COPD. A proposed mechanism for this protective effect was believed to be related to the ability of specific VDBP isoforms to increase neutrophil chemotaxis; however, Schellenberg et al (37) noted no difference in the ability of the different VDBP isoforms to attract neutrophils.

The above studies demonstrate an association between VDBP and the development of COPD. However, a conflicting study performed by Kauffmann et al (38) noted no difference in the VDBP phenotypes and risk of developing COPD. Of note, Kauffman et al (38) had studied a different patient population. Their population consisted of smokers with preserved lung function versus nonsmokers with decreased lung function, which may have contributed to their findings.

Asthma and vitamin D

Vitamin D has been linked to asthma in several animal and human studies. Wittke et al (39) demonstrated that mice selectively bred without VDRs fail to develop airway inflammation (decreased infiltration of lymphocytes and eosinophils). These same mice also lacked the expected airway hyperresponsiveness despite elevated immunoglobulin E and T helper 2 cytokine production. However, treatment with 1,25-dihydroxyvitamin D_3 has no affect on asthma severity in the wild-type mouse population (39).

Increased maternal vitamin D intake during pregnancy has been linked to a decreased incidence of wheezing during childhood. A decreased risk of doctor-diagnosed asthma or recurrent wheezing episodes at three years of age was noted in those whose mothers had higher vitamin D intake during the prenatal period (40). A similar study (41) performed in Scotland confirmed that increased vitamin D intake during pregnancy

decreased the risk of wheezing in early childhood (children were followed up to five years of age). Lower maternal intake of vitamin D was also associated with a decreased bronchodilator response in children five years of age.

Contrary to the previously mentioned studies, Gale et al (42) found that in pregnancy, maternal supplementation to vitamin D levels greater than 75 nmol/L led to an increased risk of eczema at nine months and asthma at nine years for their offspring. However, the results of this study may be challenged because greater than 60% of the children were lost to follow-up at nine years of age. The Northern Finland Birth Cohort study (43) also noted an increased risk of atopy and allergic rhinitis in patients receiving vitamin D supplementation over a 30-year period. There was a nonsignificant increase in the risk of developing asthma in patients receiving vitamin D supplementation (P=0.08). It appears that vitamin D may have a role in the development of atopy, allergic rhinitis and asthma; however, as these conflicting studies show, it is not clear as to the true effect of vitamin D supplementation.

Studies further demonstrate that asthma may be linked to vitamin D on a molecular genetic basis. Raby et al (44) and Poon et al (45) identified polymorphisms of the VDR that influence asthma and allergy susceptibility. Raby et al (46) has suggested a link, located on chromosome 12q, between asthma, airway responsiveness and pulmonary function indexes. In a different study, Raby et al (44) was able to demonstrate a genetic link between asthma and VDR located in close proximity on that same chromosome 12q. Poon et al (45) discovered an association between VDR variants and the presence of asthma and atopy in a Quebec cohort (45). This work seems to further suggest that VDRs and vitamin D may play a role on a genetic level in the development of atopic and allergic disease (44).

CF and vitamin D

There are no studies linking CF and vitamin D deficiency on a genetic basis; however, vitamin D deficiency is very common in the CF population. A recent consensus guideline reviewing bone disease and the role of vitamin D deficiency in CF has addressed some of these concerns (47). One study (48) was able to demonstrate that CF patients with decreased serum 25-hydroxyvitamin D levels had significantly worse lung function than other patients with CF.

TREATMENT OF VITAMIN D DEFICIENCY IN CHRONIC LUNG DISEASE

The Institute of Medicine (Washington, DC, USA) recommends that adults obtain an average daily intake of vitamin D ranging from 200 U to 600 U to maintain adequate vitamin D levels (49). With regard to vitamin D deficiency, experts have recommended supplementation at much higher doses, with recommendations for 28,000 U on a weekly basis or 50,000 U on a monthly basis (50) depending on the degree of deficiency. There are several studies recommending methods to replete vitamin D, which has recently been reviewed by Holick (51).

There are no specific guidelines regarding supplementation for vitamin D deficiency in chronic lung disease, except as previously mentioned in the CF population (47). Also, it appears that even if patients with vitamin D deficiency and chronic lung diseases are identified, it may be difficult to treat. Donovan et al (52) identified 20 adult patients with end-stage CF and revealed that with standard supplementation (400 U to 800 U of vitamin D), 15 still had serum 25-hydroxyvitamin D levels below 20 ng/mL (50 nmol/L). In a larger study involving both children and young adults, Rovner et al (53) confirmed the presence of inadequate vitamin D levels in patients with CF despite standard supplementation with oral vitamin D. Boyle et al (54), prospectively studied adult CF patients providing supplementation with 50,000 U/week of oral ergocalciferol for eight weeks. Only 8% (five of 66 patients) were able to achieve 25-hydroxyvitamin D levels greater than 30 ng/mL (75 nmol/L). Even high-dose supplementation does not appear to be effective in patients with CF; larger doses of vitamin D administered for extended intervals may be necessary (54). However, guidelines regarding supplementation for vitamin D deficiency in the CF population include recommendations regarding testing, supplementation and follow-up (47).

From the available evidence, it appears that patients with chronic lung disease are at risk for vitamin D deficiency, regardless of standard supplementation. Further study into the underlying mechanisms for their deficiency along with the appropriate plans for treatment needs to be undertaken.

DISCUSSION

Based on the available data, there appears to be an association between vitamin D and chronic lung diseases, with the strongest data regarding COPD and asthma. The data also suggest that in diseases such as CF, asthma and COPD, lung function may be linked to vitamin D levels. However, because of the paucity of studies in this subject, the nature of the association between vitamin D levels and lung function, along with the mechanisms behind them, have not been fully elucidated. The recent NHANES III study provides exciting information displaying the connection between vitamin D levels and pulmonary function tests. These results suggest that patients with underlying chronic lung disease may be more subject to the effects vitamin D deficiency may have on lung disease than a patient population without underlying chronic lung disease. Nonetheless, NHANES III was unable to determine a causal relationship between vitamin D and lung function because it was designed as an observational study.

The connection with vitamin D deficiency is especially intriguing given the documented relationship between vitamin D and the immune system. There are significant data to support the concept that most chronic lung diseases have an element of inflammation and immune modulation related to their pathophysiology. This patient population has increased baseline levels of proinflammatory markers that often correspond to poorer disease status. Vitamin D has been shown to reduce the rate of proliferation of numerous hematopoietic cell lines along with possessing other immunomodulatory properties. Furthermore, evidence appears to link vitamin D and decreased fibroblast proliferation (55). Vitamin D has demonstrated an ability to downregulate metalloproteinases, which are capable of degrading collagen (56). These may all play a significant role in lung remodelling in the patient with chronic lung disease.

Given the potential connection between vitamin D deficiency and chronic lung disease, vitamin D supplementation is a relatively inexpensive intervention and rarely harmful. The cost of vitamin D pills range from two to 13 cents (57). While

no specific regimens have been recommended, almost any standard vitamin D treatment is unlikely to be cost prohibitive. Along with the low cost, side effects of vitamin D supplementation are minimal, with hypercalcemia being a rare but easily managed complication (15). No signs of toxicity were evident in patients given 10,000 U of vitamin D_3 per day for five months (51).

CONCLUSION

Many questions still exist regarding vitamin D and its effect on pulmonary function. There is clear evidence to support the association of vitamin D and chronic lung diseases. Based on the available evidence, further investigations are needed to determine whether vitamin D has a direct effect on the mechanisms of lung injury and lung function. Further study could also explore whether supplementation with vitamin D offers any benefit in the prevention or treatment of chronic lung disease.

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