

Vitamin D Deficiency. What does it mean for Chronic Obstructive Pulmonary Disease (COPD)? A Concise Review for Pulmonologists

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Introduction

Vitamin D hypovitaminosis (deficiency and insufficiency) and COPD are both world-wide health problems (1-4). COPD has an increasing mortality and morbidity rate and is expected to be the 3rd leading cause of death in 2020 (2). Although there has been much progress in understanding in its pathogenesis, natural course and management, there are still many unmet needs. No current treatment has the power to cure the disease (2,5).

The first description of the vitamin D-related disease was made by Glisson in 1651. He described children with rickets, as “Morbus Anglorum”. The association between inadequate sunshine and rickets was first recognized in the beginning of the 20th century (6,7).

More recently there has been increased interest in vitamin D regarding its potential noncalcemic effects and its relationship with chronic disease, particularly COPD. There might be a possible link between vitamin D hypovitaminosis and COPD pathogenesis, progression, exacerbations and comorbidities. This raised the question as to whether vitamin D supplementation might be beneficial in COPD. This paper reviews the currently available evidence.

Vitamin D Synthesis and Metabolism

Under the ultraviolet B (290-315 nm) [UV-B] irradiation, vitamin D is synthesised in the skin as previtamin D₃, which is converted to vitamin D₃, also known as cholecalciferol. The efficiency of conversion of the previtamin to vitamin D₃ depends on the number of the UV-B photons and the degree of skin melanin pigmentation. An increase in melanin, skin cover with sunscreen or excessive clothing reduces vitamin D₃ production. Excessive sunlight exposure does not cause vitamin D₃ intoxication because sunlight destroys any excess vitamin D₃ in skin (6,8). Vitamin D₂ (known as ergocalciferol and obtained by irradiation of

plants or food) and vitamin D₃ (supplied by fortified food, diet supplement and fish e.g. herring and mackerel) are integrated into chylomicrons and absorbed through the lymphatic system. In the blood, it is carried by vitamin D Binding Protein (DBP) to the liver where it is hydroxylated to form 25-hydroxyvitamin D (25(OH) D). This is the major form of vitamin D and is used as a measure of vitamin D status in the body. In the kidney, 1- α hydroxylase converts 25-hydroxyvitamin D (25(OH) D) to 1,25-dihydroxy vitamin D (1,25 (OH)₂ D) which is the biologically active form of the vitamin. When 1,25-dihydroxy vitamin D is formed; it binds to its receptor, vitamin D Receptor (VDR) which is located in the nucleus of the target cell. In the small intestine it activates calcium and phosphorus translocation to the blood. The major action of 1,25-(OH)₂ D is to provide a sufficient level of calcium and phosphorus in circulation. If the blood level of calcium level falls, 1,25-(OH)₂ D interacts with VDR in osteoclasts to stimulate bone resorption to raise calcium and phosphorus. The main target organs of 1,25-(OH)₂ D are the small intestine, kidney and bones (6,8) (Fig 1).

In vitamin D deficiency, calcium and phosphorus absorption from the small intestine is impaired and only 10% of calcium and 50% of phosphorus can be absorbed. This results in an increase in parathyroid hormone (PTH) which stimulates the reabsorption of calcium in the kidney to preserve blood calcium level. PTH also inhibits the reabsorption of phosphorus resulting in increased urinary excretion. Hence, PTH stimulates osteoclasts to mobilize skeletal calcium to the blood in order to keep calcium level in steady. In secondary hyperparathyroidism, PTH stimulates the kidney to produce 1,25-(OH)₂ D so that the level of 1,25-(OH)₂ D may be high or normal which means that it is unreliable marker of the status of vitamin D needs of the body. Eventually, vitamin D deficiency causes impairment of mineralization of the skeleton resulting in rickets in children. However, vitamin D deficiency can be subclinical and accompanied by normal serum calcium levels, low 25(OH)-D level (10-20 ng/ml), high PTH, 1,25-(OH)₂ D and alkaline phosphatase levels (8) (Fig 1).

Definition of Vitamin D Deficiency

The level of vitamin D deficiency depends on the cut points of 25(OH) D levels. A serum level of 10 ng/ml (25 nmol/l) of 25(OH) D is considered to be the threshold for preventing rickets and osteomalacia, but the desirable level to suppress PTH activity and for many other essential noncalcemic health benefit should be above 20-30 ng/ml (9-11). In a study carried out in indoor office workers who reside in subtropical climate if the cut point was chosen as 50 nmol/L (20 ng/ml), the number of vitamin D sufficient people were 60% however if the cut point was increased to 75 nmol/L (30 ng/L), this number reduced to 13%. (12).

The US Endocrinology Society defined vitamin D deficiency as a blood 25(OH) D level below 20 ng/ml (50 nmol/l) and vitamin D insufficiency when the level lies between 21-29 ng/ml (52.5-72.5 nmol/l). 30 ng/ml is considered as desirable blood level. In the absence of adequate sun exposure, at least 800-1000 IU vitamin D per day may be needed to maintain 30 ng/ml blood level of vitamin D (9,10,13). The response to vitamin D supplementation may vary individually. Recent data showed that patient's baseline vitamin D level and the amount of supplementation were the most accountable factors in response however, genetic variability may be associated with response to supplementation, suggesting that some people might need higher doses to reach optimal 25(OH) D levels or that there is variability in the physiologically normal level of 25(OH) D (14).

Risk Factors for Vitamin D Deficiency

Vitamin D deficiency is mostly caused by inadequate exposure to sunlight and inadequate dietary intake. Natural nutritional sources are mainly limited to fatty fish, so regular sunlight exposure is still the best way to prevent and resolve vitamin D deficiency. In order to have appropriate vitamin D₃ production, direct sunlight exposure needs to be maintained for only

15 min twice a week (without wearing sunscreen) (15). Since there is a seasonal variation in sunlight, there is also a seasonal variation in serum vitamin D level which shows the highest level in summer and the lowest level in winter in the northern hemisphere (16-18). Even during the summer, early morning and late afternoon UV-B is not sufficient to activate vitamin D production in the skin (19). Hence, people who live in higher latitude have a higher risk of vitamin D deficiency. Premenopausal women have been shown to have 6 nmol/l higher serum levels compared to postmenopausal women (19). Apart from sun exposure and skin vitamin D synthesizing ability, premature birth, pigmented skin, obesity, malabsorption, glucocorticoid usage, smoking, advanced age and reduced physical activity are also risk factors for vitamin D deficiency which most of them are also risk factors for COPD (6,9,20-25).

Epidemiology

Vitamin D deficiency is under diagnosed. Depending on which cut off has been used, 57-93% of the general inpatient population was defined as deficient (16,18). In hip fractured elderly patients, vitamin D level was detected under 20 nmol/l in 80% of the people (19). In a review by Lips, in which vitamin D deficiency was defined when serum 25(OH)D was lower than 25 nmol/l (10 ng/ml) and vitamin D insufficiency was considered when serum 25(OH)D was between 25 and 50 nmol/l (10–20 ng/ml), the prevalence of deficiency was reported to be between 2-30% of adults in European countries. In Germany, in people aged between 50 to 81 years, the prevalence of deficiency was 25%. In postmenopausal women, in Italy, the prevalence was 28-32% (26).

Even though Turkey is a sunny country, people tend to under recognise it. In elderly people, another Turkish study showed that 33% had a vitamin D level under 15 ng/dl. The authors

concluded that it was related with clothing habit (27). Adults living in urban, non-coastal setting also had a high prevalence of vitamin D deficiency (28).

In Middle East countries, vitamin D deficiency showed a strong relationship with lifestyle and varies between 2-90%. Vitamin D status was better in women who wore Western style clothing than in women with a veil (1). A study from South Africa found that only 16% of the participants had 25(OH) D levels above 50 nmol/L, and 15% were below 30 nmol/L (4).

Many studies examining the vitamin D status in North-America have been published (4) and according to the most recent NHANES data, the mean serum 25(OH)D level in 4495 individuals was 49.8 nmol/l; 50.3 nmol/l in men and 49.5 nmol/l in women (29). Only few studies on vitamin D status in South-America have been published (4). In a study in Argentina, a clear North-South gradient was observed with higher vitamin D levels near the equator (30). In Chile, lower 25(OH)D levels were observed in postmenopausal as compared with premenopausal women (31), although the level in postmenopausal was very similar to the level in independently living elderly in Brazil (48.8 vs 49.5 nmol/l) (32).

In Asia, the prevalence of vitamin D deficiency is 2-65%. Eastern Ural in Russia, Mongolia, China have the highest prevalence. China also has the highest rickets prevalence in the world (1) and 50% of the children have serum vitamin D level less than 12.5 nmol/l. In India, even though it is close to Equator, deficiency is very prevalent, this may due to dark skin color and low vitamin D intake. In contrast Japan and Malaysia have low prevalence of Vitamin D deficiency; in Japan, the level of Vitamin D is correlated with fish consumption (1). Vitamin D Status in South Korea is similar to other Asian countries. The Korea National Health and Nutrition Examination Survey showed that the prevalence of vitamin D insufficiency (<50 nmol/l) was 47% in males and 65% in females in 2008 (33).

Cellular and intercellular effects of Vitamin D Deficiency

The interaction between vitamin D and VDR and 1,25(OH)₂ D production in immune cells and respiratory epithelium modulates toll like receptors (TLRs), T cell proliferation and differentiation, tumour necrosis factor alpha (TNF- α) synthesis or antimicrobial host proteins which can all effect autoimmunity and host defence (15). Vitamin D has immune-modulatory effects with several other mechanisms. Antigen presenting cells can be inhibited by vitamin D. It also inhibits inflammatory cytokine expression, such as interleukin (IL)-1, - α , -1 β , -12, TNF- α , and T lymphocyte differentiation. Vitamin D is dose dependently associated with a reduction in transcription of Th1 cytokines such as IL-2, granulocyte-macrophage colony stimulating factor (GM-CSF) and interferon (IFN)- γ and increased expression of Th2 cytokines IL-4,-5 and -10. It appears to cause over expression of Th2 cytokines, and has an anti-proliferative effect on T helper cells and a suppressive effect on B cell antibody production (34,35). One of the most significant effects of 1,25 (OH)₂ D is the impact on regulatory T cells (Tregs) which are involved in autoimmune disease, COPD and asthma. In addition to the immune cells, respiratory epithelial cells are able to convert inactive vitamin D to active 1,25(OH)₂ D. This may trigger a high concentration of vitamin D that can result in expression of vitamin D dependent genes, which are important for innate immunity (15). In activated macrophages, activation of TLR with lipopolysaccharides can stimulate the local production of 1,25(OH)₂ D which enhances the expression of the antimicrobial peptide cathelicidin, which is important for the immune response to *Mycobacterium tuberculosis*. That may explain why vitamin D deficient individuals are more susceptible to tuberculosis (8,36) (Figs 2 and 3).

Genetic defects in VDR and VDBP may produce a situation like vitamin D deficiency. VDBP is also known as Gc-globulin and located in various body fluid and many cell surfaces including human neutrophils. VDBP has three domains that have a lot of additional functions besides carrying vitamin D, especially in macrophage and neutrophils (37). These include the

augmentation of chemotactic response to complement anaphylatoxin C5a and formation of a dimeric molecule with macrophage activating factor (DBP-MAF) which changes macrophages to more phagocytic phenotype (38). The VDBP gene is highly polymorphic. There are three common variants Gc1F, Gc1S, Gc2. These variations may have a role in the pathogenesis of lung diseases including asthma, COPD, lung cancer, tuberculosis, respiratory syncytial virus (RSV) bronchiolitis and adult respiratory distress syndrome (37,39). Several polymorphisms have been shown in the VDR gene too and there are data showing a relationship between VDR gene polymorphism and tuberculosis and RSV infections (15).

Noncalcemic effects of vitamin D deficiency

It has been shown that VDR and VDBP are present, not only in the organs associated with calcium metabolism but also in some other essential organs, such as skeletal muscle, lung, brain, immune cells including monocytes, activated macrophages, dendritic cells, natural killer cells, and T and B cells, pancreas, breast, colon and heart (8,15). 3% of the mouse and human genome are regulated via vitamin D pathway (34), so deficiency may have more effects than are currently known (35). Most cells have the potential to express 1-alpha hydroxylase and so produce 1,25(OH)₂ D, however this is under the control of immune cells instead of calcium and phosphorus serum levels. VDR and VDBP activation in immune cells has potent antiproliferative, prodifferentiative and immunomodulatory functions, with both immune-enhancing and immune-suppressive effects. Due to these properties, there has been much interest in the potential noncalcemic effects of vitamin D metabolism, in particularly in autoimmune disease, cancer and infectious disease (15).

Vitamin D deficiency is associated with muscle weakness in both adults and children. In order to have better muscle function in adults, a serum level above 30 ng/ml is required. In a study carried out on both active and inactive people over 60 years of age, showed that a

vitamin D level in the range 40-94 nmol/l was best for good musculoskeletal function in the legs (40). Vitamin D deficiency has been shown to be associated with breast, colon, prostate, ovary and esophagus cancers, although it is not known whether maternal, in utero or childhood deficiency increases the future risk of cancers. Children exposed to sunlight have been shown to have 40% less risk of developing non-Hodgkin lymphoma and have better survival from malignant melanoma (8). In a prospective US cohort, it was estimated that for every 10 ng/ml increase in serum vitamin D there was a 17% reduction in overall cancer rate and 45% reduction in gastrointestinal cancers (41).

The risk of developing multiple sclerosis is 50% greater when the vitamin D level is below 20 ng/ml (35). Living at high latitude for the first 10 years of life is associated with a doubling of the risk of developing multiple sclerosis, no matter where people live after that (35). Children living in higher latitudes are more prone to developing Type I diabetes, supplementation of vitamin D can reduce that risk (42). Ulcerative colitis, Crohn's disease, rheumatoid arthritis, type II diabetes and psoriasis are also shown to have a greater prevalence with vitamin D deficiency (10,35). Skaaby et al. reported a significant inverse association between vitamin D status and death caused by diseases of the respiratory, digestive and, endocrine systems. However, no association was found with vitamin D status and death caused by neoplasms or diseases of the circulatory system (43,44).

Vitamin D Deficiency and COPD

Vitamin D deficiency is highly prevalent in chronic lung disease, but the mechanism linking the two has not been fully elucidated. Animal and laboratory studies showed substantial positive effects of vitamin D on the alveolar type II cell, fibroblast proliferation, surfactant synthesis, and alveolization (45).

Vitamin D deficiency has been shown to be more prevalent in impaired fetal lung size, childhood asthma, cystic fibrosis, respiratory infections, tuberculosis, COPD and diffuse parenchymal lung disease (10,36,46) (Fig 3).

The recent Western Australian Birth Cohort study showed that, 36% of the pregnant women had vitamin D deficiency and after adjusting other confounders, vitamin D deficiency is related with lung impairment in 6-year-old offspring (47).

Additionally, in a longitudinal study, low maternal Vitamin D level was found to be associated with asthma in the first 10 year of children (48). The causal mechanisms in these associations are not clearly known. Immune mechanisms and the possible effects on smooth muscle cell proliferation and differentiation and lung growth may cause these associations (49,50). Low birth weight is also shown to be related with the development of COPD (51).

An age-matched controlled study showed that COPD patients had significantly lower vitamin D levels when compared to controls, which might suggest that COPD patients have a higher risk of vitamin D deficiency (10,35). This could be due to low food intake, aging, staying indoors, increased vitamin D catabolism due to glucocorticosteroids, impaired activation by renal dysfunction, lower storage capacity in muscles or fat tissues due to wasting (35,52).

The Role of Vitamin D in COPD Onset

Numerous genetic and immunologic studies have been performed to investigate test for a causal relationship between vitamin D and the development COPD. There is evidence that Th1 immunity and Th17 are involved in COPD and may provide a link between vitamin D deficiency and COPD (35). Deficiency might enhance inflammation, parenchymal degradation, IL-18, TNF- α , Matrix Metalloproteinase (MMP)-9 productions, chemokine

productions (through NF- κ B), histone acetylation and corticosteroid resistance. Vitamin D also has a role in airway smooth muscle remodelling (36,53) (Fig 3).

In genetic research, certain allelic mutations in VDBP may either increase the risk or have a protective effect for developing COPD. Ethnicity may be an important factor. For instance, in many small studies, in Caucasians, Gc2 protein was found to be protective against COPD, however, in an Asian population presence of the Gc1F variant was a risk factor for COPD (39,54). Studies regarding different VDBP variants and their effects on the development of COPD are summarised at Table 1 (37). It is very challenging to dissect out the effect of vitamin D from VDBP itself, since most of the actions of VDBP are thought to be through enhancing the bioavailability of the active vitamin D metabolite.

In a recent very large general population study, 10,116 participants from Copenhagen City Heart Study and 8,391 participants from Copenhagen General Population Study were studied to test if a low plasma level of 25 (OH) D was associated with future risk of COPD. It found an association; hazard ratio: 1.58 and 2.00 for the two studies respectively (55). In a very recent Danish study performed in 12,041 individuals with an average of 9.7-year follow-up, a statistically significant inverse cross-sectional association was found between vitamin D status and prevalent COPD but not with incident COPD (44).

Calcemic Effects in COPD

In the National Health and Nutrition Examination Survey (NHANES) III study, in 9,502 participants, airflow limitation was independently associated with an increased odds ratio (OR) for osteoporosis (OR: 1.9). In severe airflow obstruction, this OR reached 2.4 and the observation was true for both women and men. The study highlighted that, in moderate to severe COPD, osteoporosis should be actively sought (56).

In Towards a Revolution in COPD Health Study (TORCH) in a posthoc analysis conducted in 658 patients, almost 50% of the patients had osteoporosis or osteopenia regardless of sex (57).

Currently the overall prevalence of osteoporosis defined by low bone mineral density was 35.1% on average, ranging from 8.7% to 69% more occurred in ill patients and patients with exacerbation. As a consequence, prevalence of morphometric vertebral fractures in COPD patients has been reported to be 24%–79% (58).

Osteoporosis could be related with many parameters of lung functions. In a study performed in 49 COPD patients, patients with osteoporosis had a significantly lower (BMI) and higher residual volume (RV) as the percentage of total lung capacity (RV%TLC) compared to COPD patients without osteoporosis (59).

Osteoporosis in COPD may result from several conditions that eventually ended up with vitamin D deficiency and bone resorption. People with COPD tend to be older, physically less active, more home-bounded and with less muscle bulk, which all result in less vitamin D production. As a major cause of osteoporosis, vitamin D deficiency should be checked in COPD actively, and replacement therapy should be considered in patients who are deficient (35).

Noncalcemic Effects in COPD

As mentioned previously, 1,25 (OH)₂ D has antimycobacterial, antibacterial and antiviral effects through various mechanisms. Antimicrobial polypeptides such as cathelicidin are genetically under the control of vitamin D response element (VDRE)-containing promoters. Cathelicidin functions against mycobacterium and a number of antibiotic resistant strains such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, different viruses and,

chlamydia. Those actions have a particular importance due to the fact that infectious exacerbations influence COPD disease progression (35,36,53).

Remarkable number of human studies have indicated the clinical association of vitamin D deficiency and respiratory infections. In a Finnish study, conducted in 800 healthy males, subjects with serum 25(OH)D concentrations < 40 nmol/L had significantly more days of absence from duty due to respiratory infection (60). In a study carried out in 2135 patients with prehospitalization vitamin D measurement, patients with vitamin D < 10 ng/ml had 2.33 times more hospital acquired bloodstream infection (61). There is also data regarding the association of viral infection and vitamin D deficiency. Both conditions occur more frequently in winter time and intervention on vitamin D deficiency may improve outcome of respiratory infections (62). In a post- hoc analysis of Randomised Evaluation of Calcium and/OR vitamin D (RECORD) trial, conducted in 5292 patients, patients received either placebo or 800 IU vitamin D and there was tendency of fewer self-reported infections and antibiotic usage but this was not statistically significant (63).

There are few data to suggest that vitamin D may be associated with frequent exacerbations, colonization and bacterial eradications (35,36,53). In a study originally designed to investigate the effect of daily azithromycin on COPD exacerbations, Kunisaki et al, did not find an association of vitamin D level and time to first exacerbation or number of exacerbations. In that study, the vitamin D insufficiency was present in only 33% of the patients (64). In 97 COPD patients, Wedzicha et al., tested whether vitamin D level and VDR polymorphism were associated with exacerbations, human rhinovirus (HRV) susceptibility and outdoor activity. They found that low 25-hydroxyvitamin D levels in COPD were not associated with frequent exacerbations and did not increase susceptibility to HRV exacerbations, however, independent of day length, patients who spent less time outdoors had lower 25-hydroxyvitamin D concentration (65). In a Bulgarian study, conducted during

COPD exacerbation, the entry level of vitamin D is correlated with pulmonary function tests, dyspnoea level and hospital length of stay but not exacerbation number in the previous year (66).

In a recent longitudinal study, 77% of the COPD patients coming from a Primary Care setting showed vitamin D deficiency. After adjustment for effects of supplementation and stratification according to the level of vitamin D, there was no difference in exacerbation rate and mortality (67). More recently 426 COPD patients in Norway was followed for 3 years and the relation with the vitamin D level at the study entry and exacerbation rate and mortality was evaluated and found no significant effect (68). In an Italian study conducted in 97 COPD patients, vitamin D deficiency was independently related with frequent exacerbation and hospitalization in the preceding year (69).

A very recent meta-analysis showed that low levels of serum vitamin D detected in exacerbated patients compared to stable COPD patients, however vitamin D deficiency was not found to be associated with increased risk of COPD exacerbation (70).

Based on the current data, there is no enough evidence to support the association between vitamin D deficiency and COPD exacerbation.

Pulmonary Function in COPD and Vitamin D Deficiency

The strongest evidence for a connection between vitamin D deficiency and pulmonary function comes from NHANES III. This cross sectional study showed a strong association between vitamin D levels and forced expiratory flow in one second (FEV₁) and forced vital capacity (FVC). There was a 126 ml and 172 ml mean difference in FEV₁ and FVC respectively between the patients with lowest and highest quintile of vitamin D levels (71). After adjustment for amount of leisure time activities, milk and antioxidant intake and dietary intake, the differences were less but still significant, at 106 and 142 ml, respectively. When

inactive patients excluded from the analysis the difference was still significant: 127 ml in FEV₁ (10,70). Jansens et al. showed that vitamin D deficiency was more common (60-77%) in patients with COPD (35) compared with smokers with normal lung function (31%). The serum vitamin D level was independently correlated with FEV₁ ($r=0.28$, $p<0.0001$). Additionally, vitamin D level was 25% lower in homozygous carriers of rs7041 at-risk T allele ($p<0.0001$). Logistic regression analysis showed that people with rs7041 T allele exhibited a 2.11 times greater risk for COPD (72).

In a longitudinal nested, case-control study in the Lung Health Study 3 cohort, baseline 25(OH) D levels were compared between rapid and slow lung function decliners. There was no significant difference in baseline 25(OH)D levels (25.0 vs. 25.9 ng/mL) between rapid and slow decliners (73). Vitamin D insufficiency and deficiency were common among continuous smokers with established mild to moderate COPD, however; the baseline 25(OH) D levels were not predictive of subsequent lung function decline (73). In the Norway cohort, vitamin D deficient patients (<10 ng/ml) had greater FEV₁ decline when compare the others (68).

In a cross sectional study of COPD patients in the UK, a relationship was found between dietary vitamin D intake and FEV₁, FEV₁/FVC and a negative association with vitamin D intake and the presence of COPD. However, the same study failed to show any association between serum level of vitamin D and FEV₁ or a positive association with serum vitamin level and presence of COPD. VDR genotypes did not have any relationship with lung function (74). In another study in 433 COPD (GOLD grade II-IV) and 325 controls showed that COPD was associated with lower levels of vitamin D ($r=-4.34$, $p=0.001$) and COPD patients had more than 2 times risk of being vitamin D deficient (OR =2.32, $p= 0.001$), after adjusting for sex, age, body mass index (BMI), smoking, comorbidities and season. In logistic regression models, the determinants of vitamin D deficiency were identified as being worse GOLD grade for airflow limitation, obesity and current smoking (18). In a post hoc

analysis, in 498 patients drawn from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) cohort, vitamin D level was found to correlate with FEV₁ (p=0.01) and computerized tomography (CT) emphysema score (p<0.01), VDBP did not show a correlation, although Vitamin D level was inversely correlated with VDBP (p=0.01). In the same study, Vitamin D level correlated with bronchodilator response, 6 min walk distance and Clara cell protein-16 (75). Most recently, in the Copenhagen City Heart Study and Copenhagen General Population Study, it was shown for the first time that low plasma level of 25(OH)D was associated with a faster decline of FEV₁ (OR: 2.30 and 3.06 for the two populations respectively) (76). As a summary most of the studies are supported that there is a positive relation with vitamin D level and lung functions. The results of these observational vitamin D studies on pulmonary function in COPD are shown in Table 2 (55,64,71,72,74,76-79).

Skeletal Muscle Weakness in COPD

Vitamin D in the elderly is associated with reductions in not only bone mineral density but in type 2 muscle fibers (80). Observational studies report an association between vitamin D, muscle function and physical performance in the elderly. In a study conducted in Longitudinal Aging Study Amsterdam, subjects were asked if they have any difficulty in daily life physically and in the older patients, vitamin D deficiency was found to be associated with an increase in limitations at 3 years (81). Korean National Health and Nutrition Examination Survey included 2258 men and 3005 women over 50 years showed an inverse association with vitamin D level and sarcopenia in women (82).

In a meta-analysis conducted in 2009 with 8 randomised controlled trials in 2426 subjects, daily vitamin D supplementation with 700-1000 IU was found to reduce the fall risk 19%. The blood level of vitamin D was found over 60 nmol/L to reduce the risk (83). Another

meta-analysis on 45782 people, mainly elderly females, found a significant reduction in falls with vitamin D supplementation in addition to calcium administration. The effect was not related to the dose or form of vitamin D supplementation. The quality of evidence was low to moderate (84).

Although the mechanisms are not fully elucidated, skeletal muscle weakness is a crucial feature and independent parameter of mortality in COPD (85). In COPD patients, 18 to 36% of patients present with detriment of muscle mass, which is responsible for weight loss in 17% to 35% of patients. The estimated overall prevalence of skeletal muscle weakness in COPD is 20%-30% (86-88).

Several studies assessed the association with vitamin D and muscle dysfunctions in COPD. In a study that examined the association of the VDR gene and quadriceps strength, FokI common variants in the VDR gene were associated with quadriceps strength in both COPD and control subjects, whereas the BsmI polymorphism was associated with muscle strength only in COPD subjects (89). Ferrari et al. also demonstrated that maximal exercise capacity and carbon monoxide transfer capacity were positively correlated with serum vitamin D level (90).

In a post-hoc subgroup analysis of a randomized trial on vitamin D supplementation, muscle strength and exercise performance were evaluated in 50 COPD patients before and 3 months after initiating 100 000 IU/monthly vitamin D or placebo. Patients receiving vitamin D had significantly larger improvements in inspiratory muscle strength and maximal oxygen uptake. Improvements in quadriceps strength and six-minute walking distance were not significantly different from the results in the placebo group (91). In another study Lange et al. found that vitamin D deficient (<25 nmol/l) patients had a worse outcome from a rehabilitation programme, with more dropouts and worse medical condition (79). Bjerck et al. performed a

6-week vitamin D supplementation trial on COPD patients to test whether 2000 IU daily vitamin D had any effect on physical performance measured using the Short Physical Performance Battery compared to placebo. There was no discernible effect on outcome (92). In another recent study, in 104 COPD patients and 100 age- and sex-matched controls, serum vitamin D level were found to be same in both groups; vitamin D level was significantly correlated with muscle strength in controls but not in COPD. The authors suggested that vitamin D resistance may occur in COPD (93). As a summary, there seems to be no conclusive results from the existing studies that shows firmly that there is an association between vitamin D level and a benefit of vitamin D supplementation and muscle functions in COPD population. Presumably, the studies were **underpowered** to answer that specific questions and well-design studies are needed.

Prevention and Treatment of Vitamin D Deficiency

COPD has systemic consequences or associations that affect patients' health (94); Cardiovascular disease and cancers are the most significant comorbidities seen in COPD with an impact on mortality (95). Low levels of vitamin D are associated with common comorbidities of COPD (15,16,71,72) and this has led to an interest in whether vitamin D supplementation would have any beneficial effect on mortality and other outcome parameters. A recent meta-analysis of randomized control trials showed that vitamin D supplementation was associated with decreased total mortality rate (96). Zittermann et al. showed that this was not a linear association and the optimal dose range is between 75 nmol to 87.5 nmol/l (97). Although the best way to produce vitamin D is sunlight exposure, there are limitations and hazardous associated with this, so nutritional supplementation is receiving much attention. There is no worldwide consensus on optimal dietary intakes and optimal levels of serum vitamin D level. Food fortification with vitamin D2 and Vitamin D3 may

have a different effect on vitamin D serum level; in a 12-week study, vitamin D3 supplementation had the larger effect on serum level of vitamin D (19). The Institute of Medicine (IOM) suggests a level above 50 nmol/l as being sufficient. However, the International Osteoporosis Foundation and Endocrine Society suggest an optimal level of 75 nmol/l for preventing fractures in older age. This level is also required to balance serum PTH level and prevent pathological osteoid formation (19,98,99). Several attempts have been made to separate out the effect of vitamin D supplementation alone from its effects when combined with calcium supplementation, because in some studies, the beneficial effect of vitamin D has been attributed to additional calcium. In order to reach 50 nmol/l serum level, 15-20 µg daily (600-800 IU), for 75 nmol/l serum level, 40-50 µg daily (1600-2000 IU) vitamin D supplementation is needed. For the other health beneficial effects of vitamin D such as effects on diabetes, cognitive functioning, muscle functions, immune functions etc., no adequate data exist (19).

Adverse health effect of vitamin D

In 2010, the IOM defined 100 µg vitamin D as a safe upper limit. Care has to be taken about calcium intake, since a very high calcium intake may increase cardiovascular disease risk, hypercalciuria and nephrolithiasis (19). In 2012, Durup et al. reported a reverse J-shaped association between vitamin D level and all-cause of mortality in a single-center Copenhagen study. It was a retrospective observational study that analysed 247,574 subjects. During the follow-up (3.07 years), a serum 25(OH)D level of 50–60 nmol/liter was associated with the lowest mortality risk. Compared to 50 nmol/liter, the hazard ratios for all-cause mortality at very low (10 nmol/liter) and high (140 nmol/liter) serum levels of 25(OH)D were 2.13 and 1.42, respectively. Similarly, both high and low levels of albumin-adjusted serum calcium

and serum PTH were associated with an increased mortality, and secondary hyperparathyroidism was associated with higher mortality (100).

Current Recommendation for Prevention and Treatment

The recent Endocrinology Guideline for vitamin D deficiency recommends that adults above age 50 years require daily 600-800 IU vitamin D for bone and muscle health. However, in order to raise blood vitamin D level over 30 mg/dl 1500-2000 IU/d vitamin D will be needed (13). It suggests that all vitamin D deficient adults should be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d. Higher doses are needed in obese patients and patients with malabsorption syndromes. In patients with extrarenal production of 1,25(OH)2D, serial monitoring of 25(OH)D levels and serum calcium levels should be monitored during treatment to prevent hypercalcemia (13). It also recommends vitamin D supplementation for fall prevention, but does not recommend its use for any noncalcemic effects, such as reducing cardiovascular risks or death (13).

Despite these recommendations, many papers have been published to intervene vitamin D deficiency for various outcomes including prevention of osteoporosis, fractures and falls, prevention and treatment of infections, prevention of COPD exacerbations. The papers have also tested different targets of 25 (OH)D blood levels with different dosing and treatment interval. We summarized some of those evidence as follows.

Evidence showed that vitamin D supplementation reduced nonvertebral fractures and improved muscle strength was suggestive but not clearly convincing (101). Additionally, in a recent study lowest quintile and the highest quintile of blood vitamin D level (<36 nmol/l and >72 nmol/L) showed the highest risk of fracture indicating the 60 to 72 nmol/L as the best

target for blood level in elderly men (102). Therefore, the existing target for calcium hemostasis (50-75 nmol/l) is also valid for reducing fall and fracture risk with the current data (103).

In regards with infectious outcomes, a higher blood level of vitamin is required. The Australian Health Authority recommends 95 nmol/L serum 25 (OH)D concentration for prevention of respiratory infection (104). Vitamin D supplementation has promising effects in several studies on prevention of respiratory infection however there is inconsistency causing difficulties to draw a definitive conclusion (105). In a recent study, an addition of intermittent bolus-dose vitamin D3 supplementation to a daily low-dose regimen did not enhance protection against acute respiratory infection in older adults and their carers. The intervention was associated with increased risk and duration of upper respiratory infection. Large intermittent oral boluses of vitamin D supplement has been hypothesised to dysregulate vitamin D metabolism in extrarenal tissues by causing inappropriately low 1-alpha-hydroxylase activity coupled with inappropriately high 24-hydroxylase activity, which may limit local concentrations of the active vitamin D metabolite 1,25-dihydroxyvitamin D. It has also been suggested that 'parent vitamin D3' (cholecalciferol) may itself play an important physiological role since the half-life of this compound is only ~24 h, daily dosing with 400 IU would have caused sustained elevation of cholecalciferol levels, whereas dosing at 2-month intervals would not have (106-108).

In a very recent study, Zittermann et al. suggested protective effect of vitamin D supplementation for acute respiratory infection for individuals with deficit or insufficient vitamin D. They recommended daily administration of 1000 IU daily vitamin D instead of high dose bolus administration starting with early autumn to cover winter time (109).

COPD is the main focus of this review. There are two large studies on COPD and vitamin D supplementation: Lehouck et al. conducted a one year, single-center, randomized, double-blind, placebo-controlled study to test the effect of monthly 100,000 IU vitamin D supplementation on exacerbation rates in 182 COPD patients. It increased the serum vitamin D level when compared to placebo, but the median time to first exacerbation, exacerbation rates, FEV₁, hospitalisation, quality of life and death did not differ between groups. However, a post-hoc analysis carried out in 30 patients with severe vitamin D deficiency (≤ 10 ng/mL) at baseline showed a significant reduction in exacerbations in the vitamin D group (110).

More recently, Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO) study has been conducted to evaluate several COPD related outcomes. 240 COPD patients were randomly allocated to the vitamin D3 and placebo groups. Vitamin D3 supplementation did not affect time to first moderate or severe exacerbation or time to first upper respiratory infection. Prespecified subgroup analysis showed that vitamin D3 was protective against moderate or severe exacerbation in participants with baseline serum 25-hydroxyvitamin D concentrations of less than 50 nmol/L. Baseline vitamin D status did not modify the effect of the intervention on risk of upper respiratory infection (111).

Conclusion;

Both vitamin D and COPD are worldwide health problems. Vitamin D has been known for a long time to be related with bone and muscle health. However, evidence has accumulated that more attention should be paid to its noncalcemic effects, particularly in chronic disease. In COPD, research to date has resulted in conflicting data and without concrete conclusions. We do not know if vitamin D deficiency is a risk factor for COPD onset or progression even though vitamin D deficiency is very prevalent in COPD patients and higher than non-COPD population. There might be common risks factors for COPD severity and vitamin D

deficiency. More severe COPD patients tend to stay home and are physically less active, which are also risk factors for vitamin D deficiency. Vitamin D has been shown to be related to many conditions associated with COPD, such as osteoporosis, muscle weakness, infection and cardiovascular disease. This may provide a beneficial effect in preventing falls in addition to preventing and treating osteoporosis. We lack any firm data to recommend higher doses of supplementation to prevent COPD onset, progression and exacerbation. There is more future research to test whether vitamin D supplementation has any beneficial effects on COPD associated comorbidities and overall quality of life and mortality.

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Table 1.GC polymorphism and the risk of chronic obstructive pulmonary disease (COPD) (37).

Population		Phenotype	No cases/controls	of Risk allele	Protective allele
Caucasian	Canada	COPD	75/64	-	GC2
	Canada	COPD	104/413	-	GC2
	Iceland	COPD	112/183	-	-
		Chronic Bronchitis	48/183	GCIF	GC2

	Russia	COPD	298/237	-	-
	USA	COPD	127 families and 304/441	-	-
	Denmark	Rapid decline of FEV ₁	283/308	-	-
Asian	Tatar	COPD	298/237	GCIF	GC2
	Japan	COPD	113/88	GCIF	-
		Rapid decline of FEV ₁	86/21		
		Emphysema	85/88		
	Japan	COPD	63/82	GCIF	-
		Diffuse Panbronchiolitis	82/82		
	China	COPD	69/52	GCIF	-

Table 2: Observational studies on Vitamin D and lung function (55,64,70,71,73,75-78).

Reference	Design	Dietary intake methodology/nutrient assessment method	Outcomes	Association
Afzal et al⁵⁵	Prospective cohort study of Danish general population initiated in 1976–1978 with follow-up examinations in 1981–1983, 1991–	Serum 25(OH)D levels	FEV ₁ , FVC	An association of lower plasma 25(OH)D levels with faster decline in lung function and with a higher risk of COPD in prospective analyses.

	1994 and 2001–2003.				
Kunisaki et al ⁶⁴	Longitudinal study of 973 participants with COPD in a 1-year study, and baseline 25(OH)D levels were compared with risk of COPD exacerbation, case-control study of 196 smokers in the Lung Health Study 3 cohort	Serum 25(OH)D levels	25(OH)D	Acute exacerbations of COPD, rate of decline in FEV ₁ over 6 years	No association between baseline levels of 25(OH)D and risk of exacerbations; baseline 25(OH)D levels were not predictive of decline in lung function
Black and Scragg ⁷⁰	Secondary analysis of NHANES	Serum 25(OH)D	25(OH)D	FEV ₁ , FVC	After adjustment for confounders, 25(OH)D levels were associated positively with FVC (p< 0,001) and FEV ₁ (p<0,001)
Janssens et al ⁷¹	Cross-sectional analysis of 414 ex-smokers older than 50	Serum levels, polymorphisms	25(OH)D, DBP	FEV ₁ , FVC	In subjects with COPD, 25(OH)D levels were associated with FEV ₁ (p<0,0001)

	years					
Shaheen et al⁷³	Cross-sectional	FFQ for vitamin D intake	FEV ₁ , FVC, dx of COPD	Total vitamin D intake associated positively with FEV ₁ (p=0,007) and FEV ₁ /FVC (p=0,02) associated negatively with COPD (OR, 0,57; 95% CI, 0,38-0,87; p=0,02)		
Shaheen et al⁷³	Cross-sectional analysis of 2943 subjects 59-years-73 years of age in the Hertfordshire Cohort Study	Serum 25(OH)D levels, vitamin D intake per FFQ; vitamin D receptor polymorphisms	FEV ₁ , FVC	No association between serum 25(OH)D and lung function		
Wood et al⁷⁷	Cross sectional study of 471 subjects with α 1-antitrypsin deficiency, 140 subjects with COPD, and 480 control subjects	Serum 25(OH)D levels, DBP levels, and single nucleotide polymorphisms in the DBP gene	Phenotypical characteristics and alveolar macrophage activation	25(OH)D levels related positively to FEV ₁ (p=0,04); DBP levels related inversly to FEV ₁ (p=0,02)		
Lange et al⁷⁸	626 men from the	Serum 25(OH)D levels	Lung function and decline in	A significant difference was found		

Normative Aging Study had 25(OH)D levels measured at 3 different time points between 1984 and 2003 with concurrent spirometry	lung function over time	with a greater effect of pack-years of smoking on FEV ₁ decline in those with vitamin D deficiency (p=0,02)
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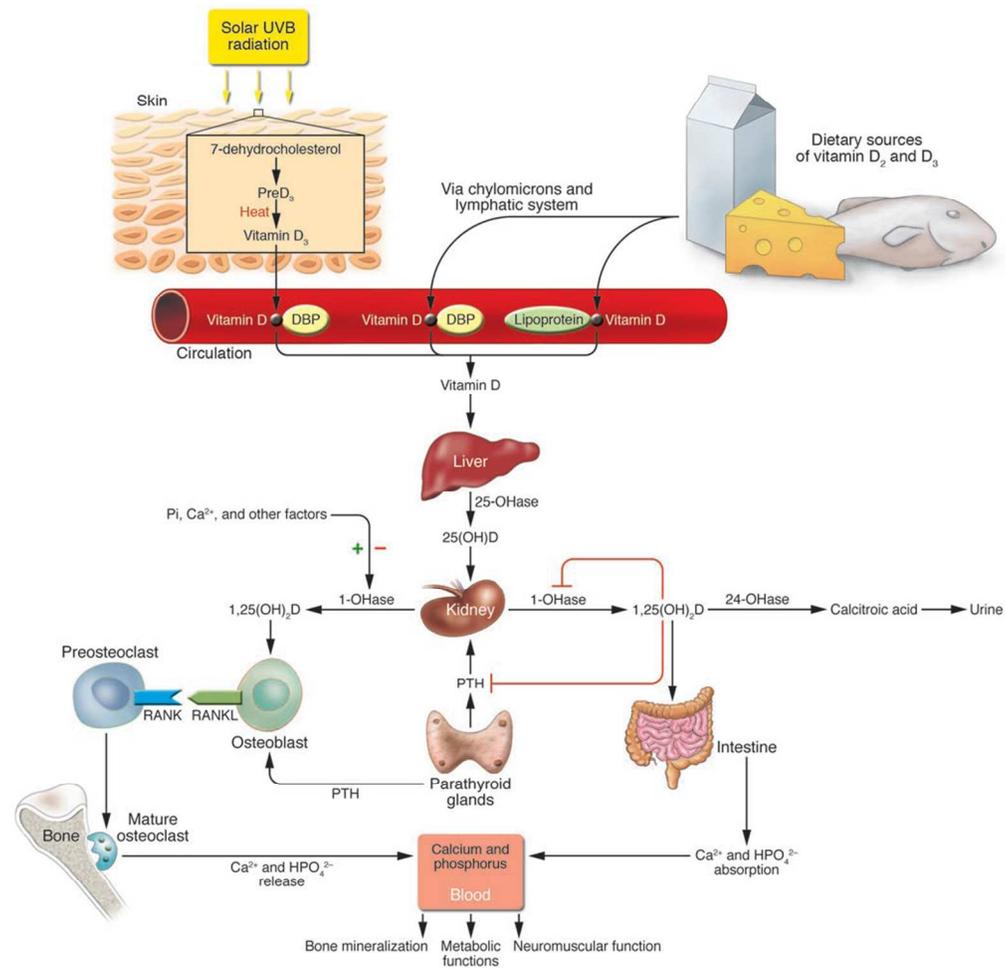


Figure 1
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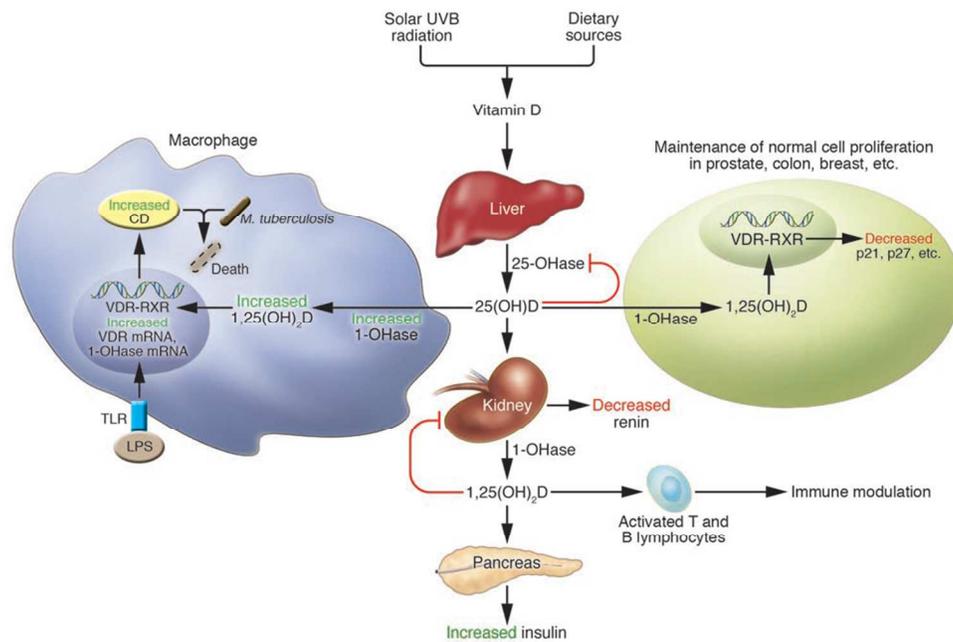


Figure 2
119- Figure 2 Noncalcemic func

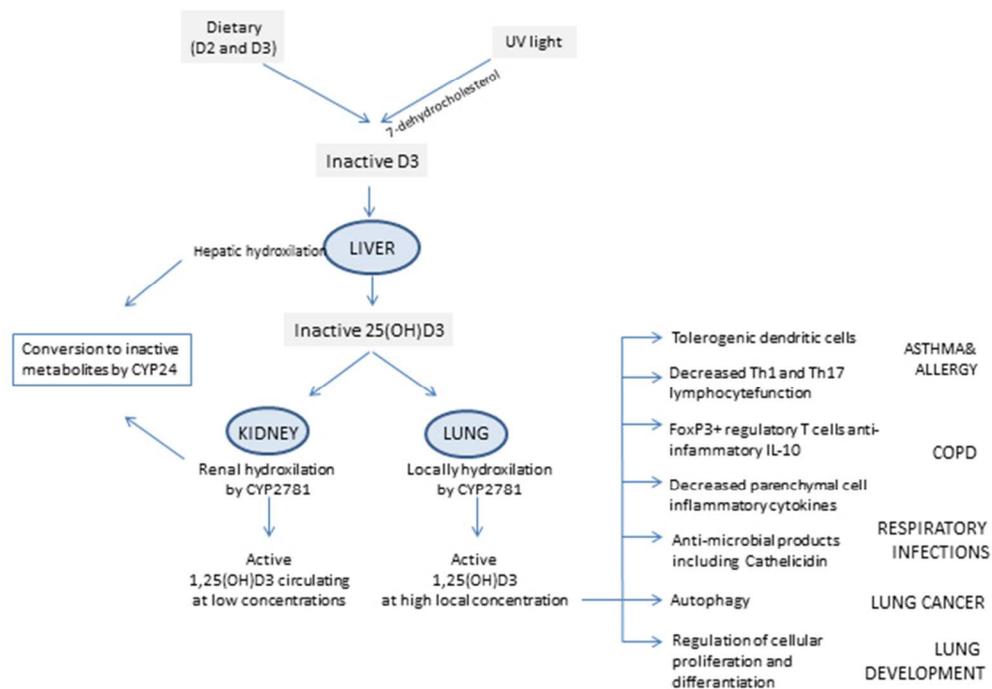


Figure 3
Noncalcemic effects of Vitamin

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