REVIEW ARTICLE

Vitamin D supplementation in respiratory diseases: evidence from randomized controlled trials

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KEY WORDS

pulmonary disease, therapy, vitamin D, vitamin D supplementation

ABSTRACT

Pulmonary diseases are one of the most important causes of morbidity and mortality. Although vitamin D is best known for its role in calcium, phosphorus, and bone homeostasis, it has gained attention in the recent years because of a wide range of extraskeletal effects, including its immunomodulatory and antibacterial potential. Vitamin D deficiency is highly prevalent in chronic pulmonary diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, tuberculosis, and asthma, and several clinical studies have been conducted investigating the effect of vitamin D supplementation on disease outcomes. In this review, we searched for positive evidence on vitamin D supplementation from randomized controlled trials and elaborated on the optimal serum vitamin D levels and dosing regimens for an effective intervention. While vitamin D supplementation seems to be beneficial as an add-on treatment for adult patients with asthma and a potent intervention to reduce exacerbations in patients with COPD, there is little evidence for its therapeutic use in cystic fibrosis, pneumonia, and tuberculosis.

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Received: October 26, 2017.
Revision accepted:
October 26, 2017.
Published online: November 3, 2017.
Conflict of interest: WJ is holder of the AstraZeneca chair in pathophysiology of respiratory diseases and is senior investigator of the Research Foundation–Flanders (FWO).
Pol Arch Intern Med. 2017;
127 (11): 775-784
doi:10.20452/pamw.4134

Introduction Pulmonary diseases such as chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis (CF) are an important cause of morbidity and mortality. As these diseases cannot be cured, current therapeutic strategies focus on symptom control and aim to limit disease progression by blocking inflammation and preventing infections. Although different strategies have been developed that reduce inflammation and improve bacterial and viral clearance, there is still a need for new effective therapies.

Vitamin D is most known for its role in bone homeostasis by regulating calcium and phosphorus metabolism.[1] Over the last decades, it has become apparent that vitamin D also exerts noncalcemic effects. The vitamin D receptor (VDR) and vitamin D-regulating enzymes are expressed in multiple cell types, including cells that are not involved in bone homeostasis. Approximately 3% of the human genome (more than 200 genes) is regulated by vitamin D.[1-3] Many of those genes are involved in noncalcemic pathways. These so called noncalcemic effects of vitamin D include an increase in insulin production, a decreased renin synthesis and an increased skeletal muscle strength, but also numerous immunomodulatory effects controlling immune activation on one side and enhancing anti-infectious defense on the other.[2]

Vitamin D deficiency is highly prevalent in the overall population. In Europe, 42% of all adults are considered to be vitamin D deficient, with 25(OH)D levels below 20 ng/ml.[4] Vitamin D deficiency is even more present in patients with pulmonary diseases such as COPD, asthma, and CF.[5-7] Given the possible immunomodulatory effects of vitamin D and the important fraction of patients with severe vitamin D deficiency in these diseases, multiple studies have tested the effect of vitamin D supplementation on clinical outcomes. In this review, we will discuss most of the randomized placebo-controlled vitamin D intervention studies to determine which patients with pulmonary diseases may benefit from vitamin D supplementation.

Vitamin D pathway Most vitamin D is produced in the skin by conversion of 7-dehydrocholesterol

into previtamin D under the influence of ultraviolet light and then isomerizes to vitamin D.[8] It can also be taken up by dietary intake through, for example, fish oils or oral supplements. Vitamin D has to undergo the first hydroxylation step in the liver by the 25-hydroxylase (CYP2R1) to form 25-hydroxyvitamin D [25(OH)D].[8] In circulation, 25(OH)D is mostly bound to vitamin D-binding protein, which increases stability and facilitates vitamin D transport, but also has immunomodulatory function.[9,10] Subsequently, 25(OH)D has to undergo the second hydroxylation step by 1α-hydroxylase (CYP27B1) to form the biologically active 1,25-dihydroxyvitamin D [1,25(OH)2D]. It mostly occurs in the kidney, but other cell types like epithelial cells and macrophages can also locally convert 25(OH)D to $1,25(OH)_2D$.[2] CYP27B1 is tightly regulated, but regulating factors differ between renal and extrarenal CYP27B1. Renal CYP27B1 is inhibited by $1,25(OH)_2D$, fibroblast growth factor 23, calcium, and phosphate and is stimulated by parathyroid hormone. Extrarenal CYP27B1 seems unresponsive to $1,25(OH)_2D$, thereby intercepting with the negative feedback loop. In some epithelial cell types, tumor necrosis factor α and interferon γ are also able to induce CYP27B1.[11]

Binding of $1,25(OH)_2D$ to the ligand-binding domain of VDR causes a heterodimerization of VDR with the retinoid X receptor (RXR). The VDR–RXR heterodimer then translocates to the nucleus and binds to specific DNA-sequences or vitamin D responsive elements in the promotor region of target genes, although sometimes far away from the start of the transcription site. Depending on the gene, gene transcription is either induced or repressed by the attraction of coactivators or corepressors, respectively. $1,25(OH)_2D$ not only affects transcription of target genes, but also acts as its own negative regulator by inducing its own catabolizing enzyme 24-hydroxylase (CYP24A1), which catabolizes not only $1,25(OH)_2D$ but also 25(OH)D into inactive metabolites.[2]

The discovery of the presence of VDR, CYP27B1, and CYP24A1 in airway epithelial cells and alveolar macrophages was the first evidence for a potential role of vitamin D in the airways. Hansdottir et al[12] showed that human respiratory epithelial cells were able to produce active vitamin D and suggested a potential role for vitamin D in host defense, because $1,25(OH)_2D$ was able to induce cathelicidin, an antimicrobial peptide.[12] The latter was confirmed in THP-1 macrophages by Liu et al[13] and recently by Heulens et al[14] in monocyte-derived macrophages from patients with COPD. VDR and the hydroxylating enzymes are also widespread among immune cells, which led to a large research field investigating the role of vitamin D in immunity and diseases.[3,14]

The vitamin D status in humans is determined by measuring circulating 25(OH)D levels, because the half-life of $1,25(OH)_2D$ is relatively short compared with that of 25(OH)D.[15] Although the debate on the appropriate levels of 25(OH)D is still ongoing, most studies define the levels of less than 20 ng/ml (50 nmol/l) as deficient because they are associated with chronic diseases.[5] This is also the threshold used in most governmental guidelines for vitamin D.[16] The levels below 10 ng/ml (25 nmol/l) are considered as severe deficiency because they are associated with an increased risk of rickets or osteomalacia. It is also assumed that patients with these levels exhibit a true risk for infections and chronic diseases.[17] Other research groups reported that the serum 25(OH)D concentrations of 30 ng/ml (75 nmol/l) or even higher, as found in native populations living around the equator, are needed for optimal health.[5,10]

Importance of vitamin D in pulmonary diseases Vitamin D deficiency is associated with multiple diseases such as cancer, hypertension, and autoimmune diseases, but also with several lung diseases.[5] A recent meta-analysis demonstrated that vitamin D levels are significantly lower in patients with tuberculosis (TB) compared with controls (apart from the African population).[18] About 70% to 90% of patients with TB have 25(OH)D levels below 20 ng/ml.[19,20] Janssens et al[6] demonstrated that patients with COPD had significantly lower 25(OH)D levels compared with healthy smokers and that vitamin D deficiency correlated with disease severity. While 31% of the healthy smokers were vitamin D deficient, this percentage increased gradually to 60% in stage 3 of COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) to even 77% in the most severe stage of the disease.

Vitamin D deficiency is also highly prevalent in CF. Up to 75% of adults and 95% of pediatric patients with CF are vitamin D deficient,[21-23] despite routine oral supplementation.[24] In patients with CF, vitamin D deficiency seems to be associated with a decreased pulmonary function in adults,[25,26] but not in children.[24,27] Moreover, Bener et al[28] revealed that vitamin D deficiency was more common in asthmatic children (52.9%) compared with healthy children (35.5%). Also in interstitial lung diseases, there is a high prevalence of vitamin D deficiency, with clear correlations between 25(OH)D levels and a reduced lung function.[29] It is not clear whether vitamin D deficiency is more common in patients with pneumonia compared with controls. Although Muhe et al[30] identified a higher incidence of vitamin D deficiency in children with pneumonia compared with controls, other studies did not confirm these results.[31,32]

There are multiple reasons for the high prevalence of vitamin D deficiency in patients with chronic lung diseases. The most likely explanation is that people who are severely ill and have a limited exercise capacity spend less time outdoor and have less sun exposure. Secondly, vitamin D deficiency can be caused by a reduced food intake or, more specifically, a reduction in

fatty fish consumption. Particularly in patients suffering from severe respiratory illness, financial means and energy to sustain a healthy diet are often missing. CF can be associated with pancreatic insufficiency, which affects absorption of fat-soluble vitamins A, D, E, and K and may lead to severe deficiency despite oral supplementation.[8] In addition, an increased catabolism or a decreased vitamin D synthesis due to aging or inflammatory processes can reduce 25(OH)D synthesis in the skin.[33,34] In many lung diseases, patients are treated with steroids, which may further impair vitamin D status through catabolic pathways.[35] Finally, polymorphisms in vitamin D-related genes may affect 25(OH)D levels. For example, in COPD, 2 variants in vitamin D-binding protein, rs7041 (TT carriers) and rs4588 (AA carriers), were associated with significantly lower 25(OH)D levels.[6]

Although vitamin D deficiency is highly prevalent in lung diseases, the question remains whether it is a consequence rather than a direct cause of the disease. One way to explore this question is to see whether vitamin D deficiency enhances the risk for an incident disease in a prospective follow-up design. For instance, a significant association between low 25(OH)D levels and a more rapid decline in lung function has been documented in several prospective cohort studies.[36-38] In addition, Afzal et al[37] linked lower 25(OH)D levels with the risk for developing COPD. In asthma, Camargo et al[39] found a significant inverse correlation between maternal vitamin D intake and wheezing in children at 3 years of age.

Another approach to investigate causality is through genetic studies. Genetic polymorphisms in key enzymes of the vitamin D pathway have been associated with an increased risk for asthma, COPD, and TB.[6,40] In particular, polymorphisms in the *VDR* gene are proven risk factors for asthma.[41] A recent meta-analysis also showed that homozygosity for the FokI polymorphism of the *VDR* gene is associated with an increased risk for TB.[40] Homozygosity for the T allele of the rs7041 variant in the vitamin D-binding protein gene increased the risk of COPD.[6] A final proof for causality is to be expected from intervention studies. As vitamin D deficiency cannot be imposed by interventions, reversing the negative effects of vitamin D deficiency by supplementation is a potent alternative. These studies will be discussed in the following paragraph.

Vitamin D supplementation as a treatment for pulmonary diseases The compelling but indirect evidence for vitamin D in chronic respiratory diseases has led to several intervention studies investigating the effect of vitamin D supplementation. Vitamin D is mostly given as an oral supplement, but also intramuscular injections are used. For oral supplementation, either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) can be used. In a meta-analysis, Tripkovic et al[42] suggested that supplementation with vitamin D_3 is more efficacious compared with vitamin D_2 in raising serum 25(OH)D levels. When designing a study, not only the type of vitamin D (D_2 or D_3) or the route of administration should be taken into account, but also the dosage regimen. Most studies exhibit a high variability in dosage regimens, ranging from daily low-dose supplementation to high-dose supplementation once per 2 months. The discussion about which strategy should be used (continuous supplementation or pulse supplementation) is still ongoing, but a recent systematic review with meta-analysis of Martineau et al[43] revealed that patients receiving daily doses benefited from vitamin D supplementation, whereas no such effect was found when given in larger bolus doses. It is even more important to explore the target 25(OH)D levels to be achieved with vitamin D supplementation. The Institute of Medicine recommends 20 ng/ml as an appropriate target, but others suggest that the levels exceeding 30 ng/ml are to be reached. This will likely affect the dosage used in any future study design.

The next section focuses on randomized controlled intervention studies with vitamin D supplementation in pulmonary diseases. We only included meta-analyses or randomized controlled trials (RCTs). Clinical trials were searched in the PubMed database using the following terms: vitamin d, vitamin d supplementation, pneumonia, tuberculosis, COPD, asthma, and cystic fibrosis. The references of eligible articles were also screened for additional studies.

Vitamin D and tuberculosis Vitamin D has been widely used to treat TB in the preantibiotic era. Already in 1848, a study was conducted about the role of cod liver oil, which is rich in vitamin D, and sun exposure as a treatment for TB.[44] In 1998, the first modern trial was conducted in children with TB, reporting that clinical improvement was faster in children taking vitamin D in addition to rifampicin, isoniazid, and streptomycin (TABLE 1).[45] Later, Nursyam et al[46] confirmed the beneficial effect of the addition of vitamin D to standard TB medication in terms of the faster sputum conversion compared with the placebo group. The SUCCINCT study[47] showed that high-dose vitamin D supplementation on top of anti-TB drugs resulted in a faster radiographic improvement and weight gain in patients with TB. However, the study did not demonstrate a difference in sputum smear conversion rates or TB scores. In addition, low baseline vitamin D levels were found to significantly impact the response to treatment, suggesting that vitamin D can boost host immunity dependent on the initial serum levels.[47] Recently, an Egyptian group also reported that vitamin D supplementation resulted in a faster sputum smear conversion and TB score.[48]

In contrast to the studies showing the beneficial effect of vitamin D supplementation, several studies could not support these findings.[20,49,50] Wejse et al[49] did not observe a positive effect of vitamin D on TB score, weight gain, sputum

TABLE 1 Overview of clinical studies on vitamin D and tuberculosis

Author	Population	Dose of vitamin D	Study duration	Outcome
Morcos et al[45]	24 children (age, 1–13 years)	1000 IU/d, no placebo	8 weeks	Clinical improvement (X-ray + ultrasound); increase in body weight
Nursyam et al[46]	67 patients (age, 15–59 years)	0.25 mg/d for 6 weeks	12 weeks	Faster sputum conversion rate; increased percentage of radiological improvement
Salahuddin et al[47]	259 patients (age >16 years)	2 × 600 000 IU intramuscularly, 1 month apart	12 weeks	Accelerated clinical and radiographic improvement; increased host immune activation in vitamin D-deficient patients
Hassanein et al[48]	60 adults	1 × 200 000 IU intramuscularly	8 weeks	Faster sputum conversion; improvement in TB score
Martineau et al[20]	146 adults	2.5 mg at inclusion and at 14, 28, and 42 days	56 days	No effect on sputum culture conversion in overall population; faster sputum conversion in patients with the tt allele in TaqI
Wejse et al[49]	365 adults	100 000 IU at inclusion, and at 5 and 8 months	12 months	No effect on clinical outcome or mortality
Tukvadze et al[50]	199 patients (age >18 years)	50 000 IU 3 × week for 8 weeks followed every other week for 8 weeks	16 weeks	No improvement in sputum TB clearance

Abbreviations: TB, tuberculosis

conversion, or mortality. In a study by Martineau et al,[20] vitamin D did not improve time to sputum conversion in the whole study population. However, sputum conversion was significantly faster in patients with the tt genotype of the TaqI polymorphism of the *VDR* gene. In contrast to the study of Martineau et al,[20] Tukvadze et al[50] could not confirm that the tt allele resulted in a faster sputum culture conversion for patients on vitamin D treatment, but the study was significantly underpowered. An alternative explanation for the negative results in the studies of Martineau et al[20] and Wejse et al[49] may be the low dosage of the intervention.[47] A meta-analysis of 5 trials[20,45-47,49] confirmed that despite a significant increase in 25(OH)D levels, there was no beneficial effect of vitamin D as a treatment for TB.[51]

Overall, with a large heterogeneity of endpoints (sputum conversion, weight gain, clinical improvement) and dosing regimens, it is currently hard to determine whether vitamin D supplementation is beneficial as an add-on therapy for TB. As the current combination anti-TB treatment is very effective in non–drug-resistant TB, a clinical beneficial effect of vitamin D supplementation may be hard to achieve.

Vitamin D and pneumonia Several studies have investigated the effect of vitamin D supplementation on acute pneumonia in children (TABLE 2),[52-55] which is still an important reason for childhood mortality.[56] None of these studies showed a beneficial effect of vitamin D on top of antibiotic treatment on the resolution of pneumonia.[52-54] One study demonstrated that children receiving vitamin D as an add-on therapy had a reduced risk of a second pneumonia episode in the next 90 days.[52] Gupta et al[55] reported a higher relative likelihood of pneumonia resolution in the group receiving vitamin D supplementation, but there was no difference in the number of hospitalization days, time to recovery, or on the recurrence of pneumonia. In the study of Choudhary et al,[53] additional outcomes were measured, but no significant difference could be detected for time to resolution of tachypnea, chest retractions, hypoxia, fever, inability to eat, and irritability or lethargy. A meta-analysis by Das et al[57] of the studies of Manaseki-Holland et al[52] and Choudhary et al[53] did not reveal a beneficial effect of vitamin D supplementation.

Currently, there is no clear evidence that vitamin D has a beneficial effect on the resolution of pneumonia. Perhaps the ongoing Lung VITAL study, which explores the effect of vitamin D and/or marine omega-3 fatty acid supplements on acute exacerbations of chronic respiratory disease, asthma control, pneumonia risk, and lung function (ClinicalTrials.gov identifier, NCT01 728 571), will provide the final answer.

Vitamin D and chronic obstructive pulmonary disease We conducted a single-center randomized placebo-controlled study in 182 patients with moderate to severe COPD and a history of exacerbations.[58] Patients were supplemented with 100 000 IU of vitamin D or placebo every 4 weeks for 1 year (TABLE 3). Despite the significant increase in 25(OH)D levels by vitamin D supplementation (20–52 ng/ml), no significant difference was found in the median time to the first or second exacerbation, annual exacerbation rate, survival, Chronic Respiratory Disease Questionnaire score, dyspnea, forced expiratory volume in 1 second (FEV_1), or fatigue between the group receiving vitamin D supplementation and the placebo group. A subanalysis in patients with severe vitamin D deficiency (<10 ng/ml) at baseline revealed a significant decrease in the rate of exacerbations per patient-year (risk ratio, 0.57; confidence interval [CI], 0.33–0.98; $P = 0.042$). In addition, the phagocytic capacity of monocytes was

TABLE 2 Overview of clinical studies on vitamin D and pneumonia

Author	Population	Dose of vitamin D	Study duration	Outcome
Manaseki-Holland et al[52]	224 children	100 000 IU of vitamin D_3 combined with antibiotic	90 days	No difference in resolution of pneumonia; lower risk of repeat episode within 90 days
Choudhary et al[53]	200 children	1000 (<1 year) – 2000 (>1 year) IU/d for 5 days	5 days	No difference in resolution of pneumonia, resolution of tachypnea, chest retractions, inability to feed
Rajshekhar et al[54]	96 children	1000 (<1 year) – 2000 (>1 year) IU/d for 5 days	5 days	No difference in resolution of pneumonia, duration of hospitalization, resolution of individual symptoms of pneumonia
Gupta et al[55]	324 children	100 000 IU of vitamin D_3, single dose	6 months	Higher relative likelihood of resolution of severe pneumonia in vitamin D-supplemented group; no difference in days of hospitalization, time to resolution, time to recovery; no difference in recurrence of pneumonia; similar results for vitamin D-deficient patients

increased in the supplemented group compared with placebo, particularly in the group with severe vitamin D deficiency.[58]

Martineau et al[59] designed the multicenter ViDiCO trial to explore the role of vitamin D supplementation in a larger set of patients with COPD. They predefined a subanalysis in the vitamin D-deficient group and included more patients with COPD stages 1 to 3 according to the GOLD classification, as compared with the study of Lehouck et al.[58] A total of 240 patients were randomized to receive oral doses of 120 000 IU of vitamin D or placebo every 2 months for 1 year. Similarly to the study of Lehouck et al,[58] vitamin D supplementation had no effect on the time to the first upper respiratory infection or the median time to a moderate or severe exacerbation, although patients with severe vitamin D deficiency [serum 25(OH)D levels <50 nmol/l] had a reduced risk of moderate to severe exacerbation. In addition, supplementation with vitamin D significantly decreased symptoms of exacerbations, as illustrated by a decrease in the mean peak symptom score and a lower exacerbation score after the exacerbation.[59]

Around the same time, Zendedel et al[60] showed a decrease in the number of COPD exacerbations and a significant improvement in FEV_1 in patients with severe and very severe COPD receiving vitamin D supplementation. Whether this effect was stronger in vitamin D-deficient patients is unknown because 25(OH)D levels were not measured.

More recently, Sanjari et al[61] were interested in the effect of cholecalciferol (vitamin D_3) or calcitriol [1,25(OH)2D] on pulmonary function, as compared with placebo. Patients with COPD with an exacerbation were treated for 7 days, but no effect of vitamin D supplementation was found either on FEV_1 or forced vital capacity (FVC). As patients were only treated and followed for 7 days, the impact of the intervention on future exacerbations or hospitalizations could not be evaluated.

Another multicenter double-blind placebo-controlled intervention study is currently recruiting participants (ClinicalTrials.gov identifier, NCT02122627). In this study, Rafiq et al[62] will investigate the effects of vitamin D supplementation on exacerbations in 240 vitamin D-deficient patients with COPD. In contrast to the studies of Lehouck et al[58] and Martineau et al,[59] who gave 1 dose per month or 1 dose per 2 months, patients will receive vitamin D at a dose of 16 800 IU once a week for 1 year. Furthermore, the effect of vitamin D on lung function, immune responses, and also physical functioning will be measured.

Three studies also investigated the effect of vitamin D supplementation on physical performance in patients with COPD. In a post-hoc analysis of Lehouck et al,[58] Hornikx et al[63] studied the effect of monthly vitamin D supplementation in a 3-month rehabilitation program in patients with COPD. Vitamin D supplementation resulted in a significant increase in maximal inspiratory strength and maximal oxygen uptake; a trend for an increased quadriceps strength and maximal expiratory strength without reaching significance was also revealed. In fact, these data suggested that vitamin D supplementation in respiratory diseases may also target other outcomes than the classic respiratory outcomes. Bjerk et al[64] conducted a pilot study in which participants received a daily dose of vitamin D (2000 IU) or placebo for 6 weeks. Although there was a significant increase in serum 25(OH)D levels, no improvements were found in the Short Physical Performance Battery or St George's Respiratory Questionnaire scores.[64] Another pilot study of Rafiq et al[65] did not show a positive effect on physical performance in 50 patients with COPD. However, a larger randomized placebo-controlled trial over a longer period is needed to draw a well-supported conclusion.

Currently, evidence suggests that vitamin D-deficient patients benefit from vitamin D supplementation to reduce the rate of exacerbations. The study of Rafiq et al[62] and a subsequent meta-analysis will finally address the issue of whether vitamin D supplementation in deficient patients with COPD should be recommended in a clinical setting to reduce exacerbations and improve physical functioning.

TABLE 3 Overview of clinical studies on vitamin D and chronic obstructive pulmonary disease

Author	Population	Dose of vitamin D	Study duration	Outcome
Lehouck et al[58]	182 patients with moderate to very severe COPD and history of recent exacerbations	100 000 IU of vitamin D_3 or placebo every 4 weeks	1 year	No difference in the median time to first or second exacerbation, annual exacerbation rate, survival, CRQ score, dyspnea, FEV_1, or fatigue in the overall population; decrease in the rate of exacerbations per patient-year in severe vitamin D-deficient patients; increased phagocytic capacity of monocytes in the vitamin D-supplemented group
Martineau et al[59]	240 patients with COPD	6 2-monthly doses of 120 000 IU of vitamin D_3 or placebo	1 year	Overall no effect on the time to first exacerbation or upper respiratory infection; significantly lower risk of a moderate to severe exacerbation in vitamin D-deficient patients
Zendedel et al[60]	88 patients with severe and very severe COPD	100 000 IU/month or placebo	6 months	Decrease in COPD exacerbations; increase in FEV_1
Sanjari et al[61]	135 patients with moderate to severe COPD and exacerbations	0.25 µg/d of calcitriol + 50 000 IU/d of vitamin D_3 or placebo	7 days	No effect on FEV_1 or FVC
Rafiq et al[62]	240 vitamin D-deficient patients with COPD after exacerbation	16 800 IU vitamin D_3 or placebo once a week	1 year	Study ongoing
Rafiq et al[65]	50 vitamin D-deficient patients with COPD	1200 IU/d of vitamin D_3	6 months	Increase in 25(OH)D levels; no effect on physical performance or respiratory muscle strength, 6-minute walking test, handgrip strength, exacerbation rate
Hornikx et al[63]	50 patients with moderate to severe COPD	100 000 IU of vitamin D_3 or placebo every 4 weeks	1 month – 1 year	Increase in maximal inspiratory strength; trend for an increase in quadriceps strength and maximal expiratory strength
Bjerk et al[64]	39 patients with severe COPD	2000 IU/d of vitamin D_3 or placebo	6 weeks	No effect on lower extremity physical performance (SPPB or SGRQ score)

Abbreviations: COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Disease Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SGRQ, St. George's Respiratory Questionnaire; SPPB, Short Physical Performance Battery

Vitamin D and cystic fibrosis Most studies regarding vitamin D supplementation in patients with CF have focused on increasing 25(OH)D levels, calcium balance, and bone health. These studies show that even despite supplementation, it remains hard to raise 25(OH)D levels in this population,[66-68] and that a higher dosage regimen is needed to increase 25(OH)D levels (TABLE 4).[69-72]

Two studies, one conducted in adults[69] and the other in children,[70] compared the effects of ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) on 25(OH)D levels. Both treatments resulted in a significant increase in 25(OH)D levels to overall sufficient levels in the study of Khazai et al,[69] while vitamin D levels exceeding 30 ng/ml were only reached in 66% of patients in the study of Simoneau et al.[70] While no preference for either vitamin D_2 or D_3 treatment was found in the study of Simoneau et al,[70] a preference for vitamin D_3 was found in the study of Khazai et al.[69]

A few studies also looked at the effect of vitamin D on pulmonary function or markers of inflammation in CF. In the study of Grossman et al,[71] patients with CF hospitalized for an exacerbation received a single dose of 250 000 IU, which increased the number of hospital-free days to over 6 months. In addition, a positive trend of supplementation was found for lung function recovery, 1-year survival, and a decreased number of home intravenous antibiotic therapy days. They also reported a significant reduction in the levels of tumor necrosis factor α at week 12.[73] In addition, Simoneau et al[70] investigated the effect of vitamin D supplementation on body mass index, FEV_1, and the levels of immunoglobulins G and E and C-reactive protein, but could not demonstrate any effect of the intervention, presumably due to the short duration of the study.

A recent study compared the efficacy of vitamin D_2 and D_3 supplementation in raising 25(OH)D levels as well as its effect on respiratory health in patients with CF. High-dose supplementation was needed to raise 25(OH)D levels. In addition, when combining the groups receiving vitamin D_2 and D_3 supplementation, the plasma interleukin-8 concentration decreased. Supplementation with vitamin D_3 also improved FVC, and a positive correlation was detected between 25(OH)D levels and the quality of life, as measured by the Cystic Fibrosis Questionnaire–Revised, as well as changes in FEV_1 and FVC.[72] Therefore, large RCTs in patients with CF are needed to see how high-dose supplementation may normalize 25(OH)D levels to those associated with better respiratory health.

Vitamin D and asthma In asthma, several well-conducted trials have explored the effect of vitamin D supplementation on asthma control. In 2015, Luo et al[74] published a meta-analysis of 7 studies, 3 of which were conducted in children[75-77]

TABLE 4 Overview of clinical studies on vitamin D and cystic fibrosis

Author	Population	Dose of vitamin D	Study duration	Outcome
Brown et al[66]	20 adults	Oral calcitriol, 0.5 μg twice daily for 14 days	2 weeks	Improvement in calcium balance; no change in 25(OH)D levels
Haworth et al[67]	30 adults	800 IU/d or placebo in addition to regular vitamin D_3 supplements (900 IU/d)	1 year	Trend for a reduction in bone turnover rate; no change in 25(OH)D levels
Hillman et al[68]	15 children (age, 7–13 years)	400 IU/d of vitamin D_3 + 1600 IU/d of vitamin D_3 or placebo	9 months	No effect on 25(OH)D levels, serum calcium levels, or mineralization
Khazai et al[69]	30 adults	50 000 IU/wk of vitamin D_2 or D_3	12 weeks	Increase in 25(OH)D levels for both treatments
Grossman et al[71]	30 adults	250 000 IU vitamin D_3 or placebo 48 h after admission	1 year	Increase in 25(OH)D levels, 1-year survival rate, and hospital-free days
Simoneau et al[70]	47 patients with CF (age, 6–21 years)	50 000 IU of vitamin D_2 twice a week for 8 weeks or 50 000 IU of vitamin D_3 weekly	8 weeks	Increase in 25(OH)D levels for both treatments; no change in FEV1%, CRP, IgG or IgE for both treatments
Pincikova et al[72]	16 patients with CF	5000 IU/d (<16 years old) or 7143 IU/d (≥16 years old) of vitamin D_2 or D_3, individually adjusted	12 weeks of supplementation + 8 weeks of extra follow-up	High-dose supplementation is needed to increase 25(OH)D levels; decrease in IL-8 levels in supplemented groups (vitamin D_2 and D_3); vitamin D_3 supplementation improved FVC; positive correlation between 25(OH)D levels and quality of life, respiratory score, changes in FEV_1 and FVC

Abbreviations: CF, cystic fibrosis; CRP, C-reactive protein; FEV1%, percent of predicted forced expiratory volume in 1 second; IgE, immunoglobulin E; IgG, immunoglobulin G; IL-8, interleukin 8; others, see TABLE 3

and 4 in adults[78-81] (TABLE 5). The meta-analysis could not show a beneficial effect of vitamin D supplementation on the prevention of asthma exacerbation, fractional exhaled nitric oxide levels, FEV_1%, or asthma symptoms.[74]

A more recent meta-analysis of RCTs on the use of vitamin D supplementation in asthma[82] included 9 clinical studies, 7 of which were conducted in 435 children[76,77,83-87] and 2 in 658 adults.[79,80] All studies with a follow-up of less than 12 weeks, those with no outcome other than bone health, or studies that were not placebo controlled were excluded, which led to the exclusion of 3 studies used in the meta-analysis of Luo et al.[75,78,81] Although all studies in this meta-analysis used supplementation with cholecalciferol, there was a high heterogeneity in the used dosages (500–1200 IU/d) and dosing regimens (once daily to every 2 months). Vitamin D supplementation significantly reduced the rate of asthma exacerbations treated with systemic corticosteroids (odds ratio [OR], 0.63; 95% CI, 0.45–0.88)[79,80,82,87] and tended to increase the time to first exacerbation (P = 0.052).[79,80,82] In addition, vitamin D significantly reduced the risk of patients having at least 1 emergency visit or hospitalization for an exacerbation (OR, 0.39; 95% CI, 0.19–0.78).[77,79,80,82,84,87] These effects are mainly attributable to studies performed in adults. Therefore, generalization of these results to children should be done with caution.[82] The meta-analysis could not identify a beneficial effect of vitamin D supplementation on FEV_1 or asthma control test scores.[82] Of note, 2 recent intervention studies demonstrated a positive effect on asthma control and lung function.[88,89]

The beneficial effect of vitamin D supplementation on asthma exacerbations was recently shown in a meta-analysis using individual patient data. The rate of asthma exacerbations requiring the use of corticosteroids was significantly reduced by vitamin D supplementation (adjusted incidence rate ratio, 0.74; 95% CI, 0.56–0.97; P = 0.03).[79,80,84-87,90,91]

Several trials also investigated whether vitamin D supplementation during pregnancy could decrease asthma in the offspring.[92,93] However, in these 2 RCTs, vitamin D supplementation had no beneficial effect on wheezing, although both studies may have been underpowered.[92-94]

Overall, the collected evidence points to a positive effect of vitamin D on the risk reduction of severe exacerbations, regardless of the baseline levels. An effect of vitamin D supplementation for pregnant women to reduce wheezing of their offspring could not be demonstrated.

Other lung diseases A recent meta-analysis of Martineau et al[43] explored the effects of vitamin D supplementation on acute (upper and lower) respiratory tract infections. The study was unique as it evaluated individual patient data of more than 15 000 people. It showed that supplementation is effective in reducing respiratory events in the general population (adjusted OR, 0.88; 95% CI, 0.81–0.96), particularly when delivered in daily doses (adjusted OR, 0.81; CI, 0.72–0.91) to deficient people (adjusted OR, 0.30; CI, 0.17–0.53.[43]

Conclusions Although numerous studies have shown immunomodulatory and antibacterial effects of vitamin D in vitro and in animal models,[13,14,95-97] the discrepancy remains when evaluating clinical association and intervention studies.

TABLE 5 Overview of clinical studies on vitamin D and asthma

Author	Population	Dose of vitamin D	Study duration	Outcome
Worth et al[81]	14 adults	1000 IU/d of vitamin D, 1 g/d of calcium, and 7.5 mg/kg body weight of ethane-1-hydroxy-1,1--diphosphonate	6 months	Increased bone density
Majak et al[77]	44 children (6–12 years)	20 mg of prednisone; 20 mg of prednisone and 0.025 mg of vitamin D_3; placebo	1 year	Prevention of suppression of clinical and immunological effects of steroid and allergen extract by vitamin D
Urashima et al[85]	Preschool children (6–15 years)	1200 IU/d of vitamin D_3	4 months	Reduction in the number of asthma attacks
Majak et al[86]	48 children (5–18 years)	800 mg/d of budesonide + 500 IU/d of vitamin D_3 or 800 mg/d budesonide + placebo	6 months	Significantly fewer children experiencing an asthma attack; significantly fewer children with a decrease in 25(OH)D levels; a correlation of 25(OH)D and ATAQ score; improvement in the ATAQ score and FEV_1 in both study groups; no increase in 25(OH)D levels
Yadav et al[76]	100 children (3–14 years)	60 000 IU/mo of vitamin D_3	6 months	Faster control of asthma; reduction in the need for steroids; increase in PEFR; decrease in the number of exacerbations
Lewis et al[83]	30 children (age, 6–17 years)	1000 IU/d vitamin D_3	1 year	No effect on ACT score or FEV_1; positive correlation between 25(OH)D levels and ACT score; inverse correlation between 25(OH)D levels and BMI; 50% of patients were still vitamin D deficient after treatment
Baris et al[75]	50 children	SCIT along with 650 IU/d of vitamin D_3, SCIT alone, and pharmacotherapy alone	1 year	Higher rate of inhaled corticosteroid discontinuation in allergen immunotherapy + vitamin D
Castro et al[80]	408 adults	1 × 100 000 IU of vitamin D_3 followed by 4000 IU/d or placebo	28 weeks	No reduction in the rate of exacerbation; no reduction in the rate of treatment failure
Martineau et al[79]	250 adults	6 oral doses every 2 months of 3-mg vitamin D_3 or placebo	1 year	No effect on the time to exacerbation; no effect on the time to first URTI
Tachimoto et al[84]	96 schoolchildren	800 IU/d of vitamin D_3 or placebo for 2 months	6 months	Improvement in asthma control; significantly lower proportion of patients with a peak expiratory flow rate <80% predicted in the supplemented group
Jensen et al[87]	Preschool children (age, 1–5 years)	1 × 100 000 IU of vitamin D_3 or placebo, followed by 400 IU/d of vitamin D_3 for 6 months	6 months	Increase in the number of children achieving vitamin D sufficiency; trend towards reduction in the rate of rescue oral corticosteroids
Ali et al[89]	115 adults	1 μg/d of alfacalcidol for 4 months or normal asthmatic medication	4 months	Significant improvement FEV_1 and FVC; improvement in asthma severity stage; no difference in improvement in vitamin D-sufficient vs vitamin D-deficient patients
Boonpiyathad et al[88]	87 adults	20 000 IU of vitamin D_2 every 2 days for 3 months	3 months	Vitamin D deficiency more common in asthma patients; vitamin D supplementation improved asthma control in patients with uncontrolled asthma
Kerley et al[91]	44 children	2000 IU/d of vitamin D_3	15 weeks	Decrease in missed school days due to asthma
Chawes et al[92]	623 pregnant women and their children	2400 IU/d of vitamin D_3 or placebo + 400 IU for pregnancy care	Pregnancy week 24 till 1 week postpartum, children followed for 3 years	No reduction in wheezing in offspring at 3 years
Litonjua et al[93]	881 pregnant women, 806 children	4000 IU/d of vitamin D_3 or placebo + 400 IU for pregnancy care	During pregnancy, children followed for 3 years	Nonsignificantly lower incidence (6.1%) of wheezing and asthma in children aged 3 years

Abbreviations: ACT, asthma control test; ATAQ, Asthma Therapy Assessment Questionnaire; BMI, body mass index; PEFR, peak expiratory flow rate; SCIT, subcutaneous immunotherapy; URTI, upper respiratory tract infection; others, see **TABLE 3**

The most important factor to explain the negative findings in vivo is the nonappropriate design of the clinical trial. Most studies are conducted in a relatively small sample size, in a heterogeneous population, and with no focus on the vitamin D-deficient subgroup. Moreover, intervention studies so far have been very heterogeneous in terms of the dose, dose regimen, and route of administration. Based on a large meta-analysis of individual patient data, one may say

that a daily dose in the vitamin D-deficient subgroup is probably the most efficient therapeutic approach. Several lung diseases clearly benefit from vitamin D supplementation. In adult asthma and vitamin D-deficient patients with COPD, the evidence is compelling and may be transferred to clinical recommendations or guidelines, while in other disease groups such as CF, pneumonia, and TB more and larger studies are warranted. Future studies should determine if vitamin D administration through inhalation may exert a more potent direct effect.

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