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REVIEW

Targeting Vitamin D Deficiency to Limit Exacerbations in Respiratory Diseases: Utopia or Strategy With Potential?

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Abstract
Patients with respiratory diseases such as cystic fibrosis, chronic obstructive pulmonary disease, or asthma often experience an acute worsening of respiratory symptoms, termed exacerbations. Although the course of exacerbations is disease specific, they are mostly triggered by a respiratory infection. Exacerbations often require hospitalization and are an important cause of mortality. Treatments of exacerbations aim to minimize the negative impact and to prevent subsequent events. Despite many existing therapy options, many patients do not benefit from therapy and suffer from recurrent events. Vitamin D deficiency is a worldwide problem and is extremely prevalent in these patients. Vitamin D, known for its calcemic effects, also has immunomodulatory and anti-infectious actions and can therefore be a possible agent to treat or prevent exacerbations. This review will focus on vitamin D as a potential candidate to treat or prevent exacerbations in CF, COPD, and asthma.

Keywords Vitamin D · Lung · Exacerbations

Pulmonary Exacerbations

Chronic respiratory diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and asthma are generally characterized as inflammatory airway diseases. All three are heterogeneous in both progression and underlying pathology. However, they share a common feature namely acute exacerbations of the disease that have dramatic effects on the health and well-being of the patients. Exacerbations often lead to frequent and prolonged hospital stays, rapid disease worsening eventually leading to increased mortality [1]. Definitions of acute exacerbations of chronic respiratory diseases vary according to the respiratory disease and exist based upon clinical findings. For cystic fibrosis (CF), the EuroCFCare Working group has recommended to use modified Fuchs criteria to define exacerbations of CF which include the need for additional antibiotic therapy and a recent change of at least two of the following criteria: change in sputum volume or color, increased cough, increased fatigue, malaise or anorexia, decrease in lung function by 10% or more, and increased dyspnea [2, 3]. The Global Alliance of obstructive lung disease defines COPD exacerbations as an acute event characterized by worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [4]. The Global Initiative for Asthma defines exacerbations as an episode of progressive increase in shortness of breath, cough, wheezing, or chest tightness (or a combination), accompanied by decreases in lung function [5]. However, in all cases, the definition of exacerbation includes a subjective change in symptoms. Air pollution, some specific medication, smoking, chronic stress, and other triggers have been identified to cause exacerbations, but the most important trigger for exacerbations are respiratory infections caused by viruses or bacteria [3, 6]. Pathogens enter the host by airborne transmissions (e.g., droplets or aerosols), replicate in the respiratory tract, and cause clinical worsening of symptoms (exacerbations). Common viruses infecting the human respiratory tract include the rhinovirus, the influenza virus, the respiratory syncytial virus (RSV), the parainfluenza virus or the adenovirus [7] but there are many others as well. Not only viruses but also bacteria, including *Streptococcus Pneumoniae, Moraxella Catarrhalis, Haemophilus influenzae* and with more sever disease also S*taphylococcus aureus, and Pseudomonas aeruginosa,* can be the cause of a respiratory infection [8]. The majority of exacerbations are treated with a combined regimen of antibiotics and systemic

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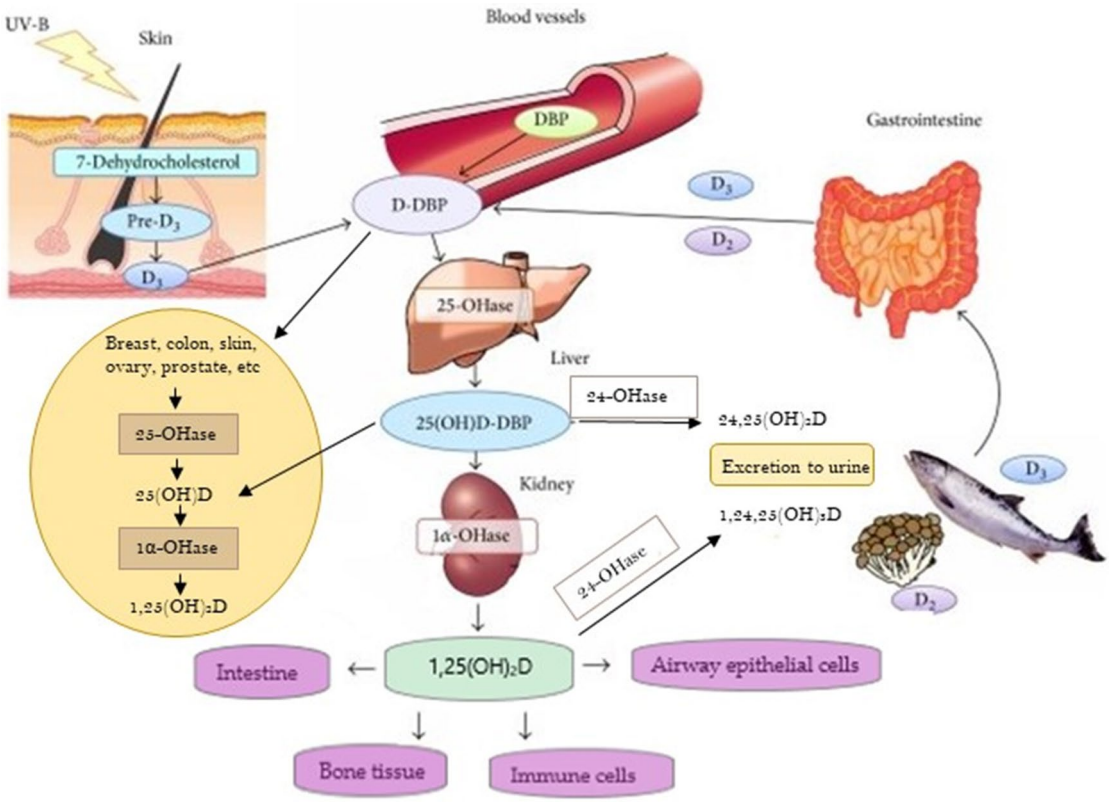

Fig. 1 Metabolism of $1,25(OH)_2D$ (Adapted from Obi et al [122] under the terms of the CC Attributions 3.0 International (CC BY 3.0) license)

corticosteroids. Although these acute treatments are proven effective, many patients suffer from recurrent events despite optimal maintenance therapy. Therefore there is an urgent need for alternative strategies to treat or prevent exacerbations. The use of vitamin D as a strategy to reduce the frequency and severity of respiratory infections in respiratory diseases is an option that deserves further consideration.

Vitamin D Metabolism and Mechanism of Action

Vitamin D is a fat-soluble vitamin essential for life and known for its calcemic effects. Vitamin D refers to two compounds, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D can be obtained from the diet or can be produced in the skin [9] (see Figure 1). It has been estimated that 80% of vitamin D supply comes from the production in the skin [10]. Endogenous vitamin D_3 is produced in the skin from 7-dehydrocholesterol through a two-step process in which pre-D_3 is first generated by UV light radiation from the sun, followed by a thermo-sensitive but non-catalytic step to form vitamin D_3 [9]. Once vitamin D is produced in the skin or taken up from the diet, it enters the circulation and is bound to the vitamin D binding protein (DBP) for transport to the liver or other tissues in which it is hydroxylated by one or more 25-hydroxylases (CYP2R1, CYP27A1, CYP3A4) into 25 hydroxyvitamin D (25(OH)D). The latter is the major circulating form of vitamin D and its plasma levels, because of its long half-life (15 days), are routinely measured as a marker of vitamin D status. The conversion to 25(OH)D is achieved primarily in the liver but can also occur in a variety of other tissues such as breast, colon, skin, ovary, lung, etc [11]. This form is, however, biologically inactive and must be converted in the kidney by 1α-hydroxylase (CYP27B1) to $1,25(OH)_2D$ which is the active form of vitamin D. The active form has a much shorter half-life (4 hours) and can therefore not be used to measure vitamin D status [12]. The activity of CYP27B1 is critical for the production and maintenance of physiologic levels of circulating $1,25(OH)_2D$ and is therefore tightly regulated. Broad studies suggest that the expression of CYP27B1 may not be restricted to the kidney but it is synthesized in other cell types as well (lung, monocytes, macrophages) [13]. In the kidney, the degradation of $1,25(OH)_2D$ is accomplished via the action of CYP24A1. Besides conversion to $1,25(OH)_2D$ by CYP27B1, 25(OH)D can also be converted to $24,25(OH)_2D$ by hydroxylation by CYP24A1in the kidney, leading to secretion into the

blood. CYP24A1 is reciprocally regulated by $1,25(OH)_2D$ itself and by parathyroid hormone (PTH) to sustain systemic levels of $1,25(OH)_2D$ [14] (Figure 1).

The direct, well-controlled, and fast actions of vitamin D in the context of calcium homeostasis have been extensively described elsewhere [15]. $1,25(OH)_2D$ also exerts genomic actions by regulating gene transcription true binding to a nuclear Vitamin D receptor (VDR) and forming a heterodimer with the retinoid X receptor (RXR), regulating in this way 3% of the human genome [13, 16, 17]. As such, vitamin D regulates genes that are linked to diverse biological processes such as cell proliferation and differentiation, cell control, apoptosis, and angiogenesis [18]. Vitamin D exerts diverse and extensive effects on the immune system, due to the expression of VDR, vitamin D metabolic enzymes, and the expression of the enzyme CYP27B1 by most immune cells, including macrophages, neutrophils, T cells, B cells, and dendritic cells [19, 20]. Also airway epithelial cells as well as immune cells in the lung express VDR. Interestingly, the expression of CYP27B1 has been detected also in pulmonary immune cells resulting in local activation of 25(OH)D in the lung [21]. In contrast to renal 1α-hydroxylation of 25(OH)D, it has been suggested that CYP27B1 in the lung is not depending on a negative feedback control of $1,25(OH)_2D$ itself [22] which might result in higher local levels of the active compound. It may indicate therefore that vitamin D can be used as an agent with immune regulatory actions in the lung and therefore be used to prevent or treat respiratory infections.

Vitamin D to Prevent or Treat Exacerbations

Vitamin D deficiency is highly prevalent in common respiratory diseases such as cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD), and asthma [23, 24]. A serum level of 25(OH)D < 25 nmol/l has been a traditional cut-off used for several decades to define vitamin D deficiency [25]. In most studies, vitamin D deficiency is defined as serum 25(OH)D levels < 20 ng/ml, insufficiency as 25(OH)D < 30 ng/ml, and sufficiency as 25(OH)D > 30 ng/ml. Based on these criteria, vitamin D deficiency is widespread across Europe [26] and the world [27] at prevalence rates that reach the criteria of a pandemic. Vitamin D status is largely determined by the level of skin synthesis and dietary intake. Vitamin D synthesized in the skin is dependent on UVB exposure and therefore influenced by latitude, skin pigmentation, skin coverage, time spent outdoors, and use of sunscreen. Dietary vitamin D can be obtained through naturally occurring vitamin D_2 or D_3 in food, dietary supplementation, or food fortification. A number of other factors such as adiposity, genetics, age, sex, and specific diseases also contribute to variation [28]. Traditional risk groups to develop vitamin D deficiency include newborns, pregnant women, older persons, and people in diseased states [27, 29]. Vitamin D deficiency was shown to be very prevalent in populations with chronic lung diseases. Fifty-nine per cent of patients with diffuse parenchymal lung diseases undergoing evaluation for lung transplant were found to have decreased vitamin D levels [30].

The respiratory tract is constantly exposed to the external environment and must therefore be well equipped to respond to and eliminate pathogens. The activation of pathogen recognition receptors (PRRs) on the respiratory epithelial cells is critical to limit viral or bacterial spread and to activate the immune system. Generally, PRR signaling upregulates cell-autonomous and non-cell-autonomous immune responses to infection. Cell-autonomous functions include the secretion of anti-microbial peptides by epithelial cells, programmed cell death, and other intracellular response pathways. Non-cell-autonomous processes are more linked to the initiation of the immune system by releasing pro-inflammatory mediators, cytokines, and chemokines [31, 32]. Vitamin D can interfere with several of these steps involved in the elimination of viruses and bacteria and in the activation of the immune system (Figure 2). First, vitamin D is involved in the regulation of the PRRs which are believed to play a crucial role in the proper function of the innate immune system. PRRs are expressed by dendritic cells, macrophages, monocytes, neutrophils, and epithelial cells. After stimulation of PRRs, a cascade of reactions is initiated that directs host defense responses such as production of cytokines and anti-microbial peptides (AMPs) [33]. Vitamin D enhances the production of AMPs such as cathelicidin and β-defensin [34, 35], which serve as a first line of defense against invading pathogens. Secondly, stimulation of PRRs also leads to induction of antigen-presenting cells to initiate the adaptive immune system. Vitamin D also modulates the adaptive immune system first by attenuating the antigen-presenting capacity of Antigen-presenting cells, such as dendritic cells and macrophages [7]. Furthermore, vitamin D was shown to enhance the phagocytic and chemotactic capacity of macrophages [19, 36] and it acts to suppress T cell-driven inflammation and enhance the effects of Tregs by increased production of anti-inflammatory cytokines (Il-10, Il-4, TGFβ) [37]. Also B cells are affected by vitamin D, as shown by decreased immunoglobulin production, proliferation, and differentiation but increased apoptosis [7].

The importance of vitamin D deficiency in respiratory infections was emphasized in observational studies that consistently reported independent associations between low serum concentrations of 25(OH)D and susceptibility to acute respiratory infection [38]. Upper respiratory tract infections (URI), mostly caused by a rhinoviral infection, are believed to be one of the major causes of exacerbations. Serum levels of 25(OH)D were shown to be inversely correlated with

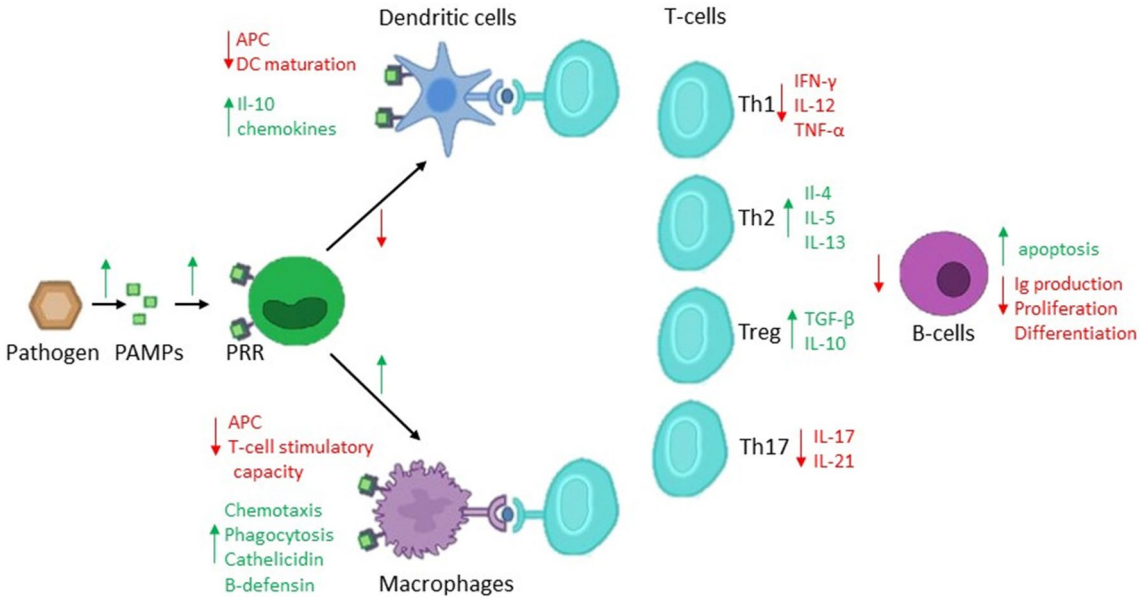

Fig. 2 Immunomodulatory actions of $1,25(OH)_2D$. Arrow down in red: inhibiting effects of vitamin D, arrow up in green: activating effects of vitamin D. PAMPs: pathogen-associated molecular patterns, PRR: pathogen recognition receptor (adapted from Greiller et al [7] under the terms of the CC Attributions 4.0 International (CC BY 4.0) license)

upper respiratory tract infections [39]. Also genetic studies confirm that polymorphism in the VDR independently associates with susceptibility to URI. Finally, in vitro studies in epithelial cell lines [40] and in human primary bronchial epithelial cells [41, 42] infected with rhinoviruses show that vitamin D is able to increase the antiviral defenses most likely via an upregulation of cathelicidin. From a mechanistic point of view, it is clear that vitamin D can be an important modulator of the host defense against respiratory infections by potentiating the clearance of pathogens while attenuating the associated inflammatory burst. As such it is important to explore vitamin D's role in the prevention or treatment of exacerbations in respiratory diseases. Detailed data on CF, COPD, and asthma will be discussed in the next paragraphs.

Vitamin D in Cystic Fibrosis

Cystic fibrosis (CF) is a common autosomal recessive disorder where a mutation in the CFTR gene results in a dysregulation of ion transport across epithelial surfaces leading to abnormally thickened mucus on the surface of the lungs. Because of the defective mucociliary clearance, bacteria cannot be eradicated and survive and proliferate leading to chronic bronchial infections. Acute pulmonary exacerbations are a very common event in CF patients and are usually triggered by respiratory viruses or bacteria. These repeated infections might lead to chronic infections and inflammation of the airways leading to progressive destruction of the lungs and respiratory failure [43]. Pulmonary exacerbations in CF have a profound impact on the morbidity and quality of life of individuals with CF [44]. Therefore efforts should be made to improve the management of these events.

Patients with CF often experience nutritional deficits, including vitamin D due to poor nutritional uptake, secondary fat malabsorption, decreased sunlight exposure, and impairment in hepatic hydroxylation of vitamin D [45, 46]. Vitamin D deficiency is common in patients with CF and prevalence ranges from 40 to 90%, depending on age and definition of deficiency [45, 47]. Treatment guidelines for vitamin D in the CF population only focus on optimizing bone health [48] and despite nutritional management recommendations, vitamin D deficiency can still be present even after supplementation [48, 49]. Associations between vitamin D status, lung function, and exacerbations are unclear. Indeed, some studies found positive associations with levels of vitamin D and lung function, as measured by FEV1 [47, 49–54] while others found no relationship [55–58]. When we focus on the relationship between serum 25(OH)D levels and exacerbations in CF, most studies reported that deficient vitamin D levels ($25(OH)D < 20$ ng/ml) are associated with more exacerbations [47, 49, 50] and more bacterial colonizations [59]. Only one large multicenter intervention study in CF has been performed trying to prevent exacerbations in CF [60]. In this study, 25,000 IU of vitamin D_3 were given to adults with CF at the time of a pulmonary exacerbations, resulting in significant increases in serum 25(OH)D concentrations remaining for the complete

duration of the study. No improvement of the time to next exacerbation or the 1-year survival was observed and there were no differences in lung function recovery or concentration of plasma cathelicidin [60]. These results are in contrast with the pilot study performed by the same group showing that bolus vitamin D supplementation (25,000 IU), improved and maintained vitamin D status and improved clinical outcomes [61].

In vitro mechanistic studies in cell lines have shown that vitamin D can be converted to its active form when topically administered to airway cells [62] while in a bronchial epithelial cell line with a CFTR mutation this ability was lost [63]. Although this loss was only observed in one particular cell line, it may suggest that the ability to convert vitamin D to its active form might be less available in CF airways. Other studies in CF respiratory cell lines showed anti-inflammatory and anti-bacterial effects after treatment with $1,25(OH)_2D$ in response to bacterial stimuli [64, 65]. Furthermore, it was demonstrated that vitamin D increased the mRNA expression of cathelicidin from primary bronchial epithelial cells collected from CF patients with no evidence for an antiviral response following a rhinoviral infection [42]. Even though mechanistic studies mostly were done *in vitro*, few studies in human suggest that the positive effects of vitamin D on exacerbations in CF are mostly attributed to its immunomodulatory properties as reflected by reduced serum IL-6, TNF levels [61], and IL-8 levels [66] or reduced serum Ig(G) levels [45]. A study on metabolomics on plasma of a supplemented CF population revealed that the beneficial effects of high-dose vitamin D in hospitalized CF adults with an acute pulmonary exacerbation may have occurred through a metabolic stabilization of amino acids, lipids, and other metabolites [67].

Based on one RCT with vitamin D supplementation in CF and the conflicting results in observational trials, it is difficult to conclude whether vitamin D can be used as an adjunctive therapy for CF exacerbations. Future investigations are needed to conclude if low-cost supplementation with vitamin D can be beneficial in preventing or treating exacerbations in the CF population. A difficult issue to address in any study in a CF population is the presence of many cofounders in this complex disease. Patients are diagnosed with the disease already at very young ages and it is known that the prevalence of vitamin D deficiency increases with age [47]. Some CF patients have poorer compliance to their medications, including vitamin D supplements and sicker patients may spend less time outdoors and may have less sun exposure or less appetite and therefore eat fewer vitamin D containing foods. These factors all contribute to the fact that studies that have addressed the relationship between vitamin D status and pulmonary function or exacerbations in CF show conflicting results.

Vitamin D in COPD and Exacerbations

COPD is characterized by airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases [68]. Smoking is the most important risk factor to develop COPD and accounts for 95% of COPD cases. COPD is complicated by exacerbations that are mostly triggered by respiratory viruses or bacteria. Studies have indicated that the quality of life and health status of patients are mainly determined by the presence and frequency of exacerbations [4]. Indeed, COPD exacerbations have important clinical and economic consequences, including lost work productivity, increased utilization of healthcare resources, temporary or permanent reductions in lung function and exercise capacity, hospitalization, and sometimes death [69]. Although the precise mechanisms of the onset of COPD exacerbations have not been fully clarified, the viral/bacterial infection-mediated immune response is thought to play a critical role.

Vitamin D deficiency (defined as serum 25 hydroxyvitamin D < 20 ng/ml) has been shown to be highly prevalent in COPD patients compared to age-matched healthy controls and increased with disease severity [24]. COPD patients are at risk for vitamin D deficiency for a variety of reasons, including unbalanced diet, absence of outdoor activity, and therefore, sun exposure and reduced capacity for vitamin D synthesis due to premature aging of the skin and smoking, increased vitamin D catabolism by glucocorticoids and lower vitamin D storage capacity [70]. Additionally, the majority of COPD patients are elderly, known to be more vitamin D deficient than the younger population. Clear associations have been found between vitamin D status and COPD. Indeed, meta-analysis reported inverse associations between vitamin D levels and COPD risk and COPD severity (Zhu 2016). Also epidemiologic studies reported a strong relationship between vitamin D levels and pulmonary function (FEV1 and FVC) [70–72]. In animal studies, vitamin D deficiency was shown to promote an early lung function decline after cigarette smoke [66], suggesting a role for vitamin D in the development of COPD. The association between vitamin D serum levels and the frequency of exacerbations is, however, still unclear [73]. In the meta-analysis of Zhu et al [74], no clear relationship was reported. In fact, two studies showed that vitamin D deficiency was related to more frequent exacerbations [75, 76], while other studies did not show such association [77–81]. Interestingly, polymorphisms in the vitamin D binding protein gene might also be related

to higher exacerbation frequencies (Ishii 2014), suggesting a relationship between vitamin D and the occurrence of exacerbations. Current strategy to treat exacerbations in COPD includes long-acting bronchodilators and long-term use of inhaled corticosteroids or macrolide antibiotics but they are all modestly effective and evidence on the preferred drug and optimal treatment duration are lacking [82]. An attractive alternative target for intervention studies in COPD is the vitamin D pathway.

Few RCTs with vitamin D supplementation aimed to prevent COPD exacerbations have been performed. A supplementation of 100,000 IU monthly for 1 year, resulting in sufficient serum vitamin D levels, showed no effect of vitamin D supplementation on the number of exacerbations. However, in a subgroup analysis of patients with severe vitamin D deficiency at baseline (25 (OH)D levels < 10 ng/ml), a significant reduction in exacerbations was observed [83]. Similar results were observed by two other studies [84, 85] and by a recent meta-analysis, including all individual patient data, confirming that the protective effect of vitamin D supplementation against COPD exacerbations is restricted to those with the lowest baseline 25(OH)D levels [86]. Two large RCTs are still ongoing and might give us more insight into the role of vitamin D in exacerbations: Lung VITAL [87] and PRECOVID [88]. The ongoing Lung VITAL study is taking advantage of a large clinical trial: VITAL, to conduct the first major evaluation of the influences of vitamin D supplementation on respiratory exacerbation in a sub-cohort enriched for active, symptomatic respiratory disease, over a period of 5 years. The PRECOVID study will be the first RCT examining the effects of vitamin D supplementation on exacerbation rate in vitamin D-deficient COPD patients. As shown in the meta-analysis of prior studies [86], the anticipated effect in this targeted subgroup may be huge.

Insights in the mechanisms of vitamin D to treat or prevent COPD exacerbations come from several mechanistic studies *in vitro*. In alveolar macrophages of smokers and non-smokers, it was shown that $1,25(OH)_2D$ inhibited the release of pro-inflammatory cytokines such as TNFα, MCP-1, and IL-6 in response to LPS/IFN-γ stimulation [36]. This was confirmed in a macrophage cell line exposed to cigarette smoke extract [36] or to LPS [89, 90]. $1,25\ (OH)_2D$ did not show any effect on the phagocytic capacity of these macrophages but it increased the levels of cathelicidin [36]. Furthermore, in venous blood samples, the rate of peripheral blood neutrophilic apoptosis in patients with acute exacerbations of COPD was slower than in healthy controls and this neutrophilic apoptosis is increased after administration of vitamin D through the p38MAPK pathway [91]. Taken together, even though in a controlled setting of cell culture, these data clearly show that vitamin D has potential to interfere with the immune reaction in response to a respiratory infection in COPD.

Vitamin D in Asthma Exacerbation

Asthma is a chronic inflammatory disease of the airway, which is characterized by airway inflammation, airway hyper responsiveness (AHR), mucus hypersecretion, and airway remodeling. The latter is irreversible and includes airway wall thickening, increased airway muscle mass, and subepithelial fibrosis, which restricts the constant airflow. Respiratory tract infections are common precipitants of acute asthma exacerbations in adults, playing a role in about 45–80% of exacerbations. Asthma mortality arises primarily during episodes of exacerbations, mostly due to viral respiratory infections, but also to exposure to particulate matter [92].

Many studies have reported high prevalence of vitamin D deficiency in asthmatic children, ranging from 50–80% worldwide [93, 94]. This was confirmed in a systematic review showing that children with asthma have lower vitamin D levels than healthy age-matched children [95]. Inadequate dietary intake, low use of vitamin D supplements, skin pigmentation, obesity, and low sun exposure all increase the risk of vitamin D insufficiency. Whether vitamin D intake during pregnancy has an impact on the development of childhood asthma is unclear as one meta-analysis found no significant association between prenatal vitamin D status and risk of asthma. However, recently, it was suggested that lower maternal vitamin D intake during pregnancy is associated with increased risk of children wheezing and being diagnosed with asthma in the first 10 years [96], indicating a role for vitamin D in the development of childhood asthma.

Vitamin D deficiency has been linked to an overall poor outcome of lung function and symptoms in patients with asthma [97–100]. Additionally, it was shown that the response to standard corticosteroid therapy was reduced in vitamin D-deficient asthmatic patients [101]. Studies in asthma also suggest an association between vitamin D deficiency and exacerbations [102, 103]. More specifically, vitamin D deficiency is associated with an increased risk for exacerbations [104]. In a 4-year follow-up study, Brehm found that vitamin D insufficiency (25(OH) D < 30 ng/ml) at baseline was associated with increased risk of severe asthma exacerbations [105]. The magnitude of this association was the greatest in children who were vitamin D insufficient and did not receive corticosteroids [94]. By contrast, Boonpiyatad et al observed that vitamin D deficiency indeed was present in patients with asthma exacerbations but could not find a causal relationship [106]. Additionally, it was shown that children who were

both vitamin D deficient and living near a major roadway were 5 times more likely to experience asthma exacerbations in comparison with children who were vitamin D sufficient and living in the same regions of high particulate matter [107]. This indicates that vitamin D deficiency represents an important factor in the development of exacerbations during asthma.

Current treatment of asthma exacerbations consists in a stepwise approach with increasing doses of medications, primarily inhaled corticosteroids (ICS), often in conjunction with a second controller medication to achieve disease control [108]. For most asthma patients, particularly those with mild-to-moderate disease, guideline-directed step care is effective resulting in symptom control and prevention of exacerbations. In severe asthma, however, this stepwise approach is not effective resulting in diminished responsiveness to treatment and need for alternative treatment strategies. As such, supplementation with vitamin D to treat vitamin D insufficiency might be an alternative strategy to prevent frequent exacerbations in asthmatic patients.

Indeed, many RCTs of vitamin D supplementation to improve asthma control and exacerbations have been completed and these studies have reported a mixture of positive and negative results. However, several meta-analyses show that vitamin D supplementation significantly reduced the rate of severe exacerbations in patients with asthma [109–113]. Whether these effects are only observed in patients with vitamin D deficiency, as was shown in COPD, is less clear since only two studies performed subgroups analysis, showing conflicting results [112, 113]. While the most recent meta-analysis clearly concluded that vitamin D supplementation played a role in reducing the rate of exacerbations particularly in patients with vitamin D insufficiency [113], subgroup analysis using individual patient data did not result in such a firm conclusion [112]. Indeed, reductions in exacerbation rate were found with vitamin D supplementations but only in participants with baseline circulating 25(OH)D levels less than 25 nmol/l and not in those with higher levels of circulating 25(OH)D (adjusted incidence rate ratio was 0.33 (95% CI 0.11–0.98) and 0.77 (95% CI 0.58–1.03), respectively). However, the p value for interaction for this subgroup analysis was not significant indicating no definitive evidence that effects of the intervention with vitamin D differed across subgroups of patients [112]. Interestingly, most intervention studies are performed in adults, while many children are suffering from asthma as well. Recent studies report that vitamin D supplementation helps in preventing the development of asthma and recurrent wheeze in early life, and may also help in the management of asthma during childhood [114, 115].

Mechanistic studies in peripheral blood mononuclear cells (PBMCs) isolated from patients with severe asthma reported an inhibition of the production of Th17 cytokines (IL-17 and IL-22), important in the pathogenesis of asthma, after treatment with $1,25(OH)_2D$ [116]. These Th17 cytokines were not inhibited by corticosteroids suggesting a steroid-enhancing property of vitamin D in asthmatic patients. In PBMCs from patients with severe asthma exacerbation and vitamin D deficiency, increased oxidative stress and DNA damage were observed compared to vitamin D-sufficient asthmatic patients with an exacerbation. In the same study, vitamin D was shown to down-regulate the expression of TNF-α, NFκB, and its phosphorylation in an LPS-stimulated airway epithelial cell line suggesting a possible mechanism for vitamin D therapy in severe asthma exacerbation [117]. Additionally, when asthma patients were treated with vitamin D, a reduction of respiratory infections was observed, and this effect was related to the increase in cathelicidin [118].

As in COPD and in CF, we should be careful in drawing conclusions concerning the role of vitamin D in asthma exacerbations. Most intervention studies are performed in adults and these results cannot be generalized to children. Still little is known about the optimal serum 25(OH)D levels to exert beneficial effects on the respiratory system. Additionally, it was observed that a rapid vitamin D supplementation (intramuscularly) compared to maintenance dose of vitamin D supplementation (orally) for children with low levels of vitamin D resulted in short- but not long-term reduction in asthma exacerbations [119].

Considerations and Future Perspectives

The relationship between Vitamin D and the respiratory system remains inconclusive. Even though most exacerbations are triggered by a respiratory infection, different pathways or mechanisms are activated with respect to the respiratory disease. Larger clinical trials and more comparable data are needed to draw conclusions on vitamin D's association with the risk of exacerbations. It is possible that failure to demonstrate an association between vitamin D deficiency and increased exacerbation risk in some studies or populations may be related to the low prevalence of participants with low baseline vitamin D levels. Indeed, mainly in COPD exacerbations, it was shown that actually only the severely deficient patients benefit from vitamin D supplementation. Moreover, even though the relationship between low serum levels of vitamin D and exacerbations remains disputable, vitamin D supplementation may still exert anti-infectious effects. Irrespective of the reasons for the discrepancy between different studies, some important issues should be taken into account when developing new clinical studies.

Currently, it is not known if aiming at sufficient serum levels of vitamin D is a good approach to benefit from the anti-inflammatory and anti-bacterial actions of vitamin D.

And if so, which serum levels can be considered as "beneficial"? Can we assume that these levels should be similar in all populations and in all respiratory diseases? Additionally, can we assume that all populations, healthy and patients, need similar oral doses to reach certain serum levels? For example, CF patients seem to require much higher doses to achieve similar vitamin D serum levels than patients with other respiratory diseases. Are circulating levels of 25(OH)D the best way to measure vitamin D status? 25(OH)D levels represent the reservoir available for the production of active $1,25(OH)_2D$ produced in the kidney by an enzymatic conversion. It is unclear how these serum levels relate to local tissue concentrations. Therefore, there are several pathways that can influence an individual's ability to produce an adequate amount of locally active vitamin D irrespective of its serum levels.

Little is known about the total dose and dose interval needed for the extra-skeletal effects of vitamin D. We speculate that the current dosing regimens and levels in interventional trials might be insufficient to fully benefit the potential actions of vitamin D. Interestingly, individual patient data analysis even revealed that daily or weekly dosing of vitamin D without additional bolus doses protected against acute respiratory infection, whereas regimens containing large boluses did not suggest that daily or weekly vitamin D administration would be a better strategy to protect against URI. This might be due to the potential adverse effects of fluctuations in circulating 25(OH)D concentrations, which are observed after bolus dosing [120]. In recent years, interest in the tolerance-inducing potential of vitamin D to modulate immune cells has grown, but one of the major obstacles for the use of active vitamin D is the need for supra-physiological doses to modulate immune responses, risking side effects such as hypercalcemia, hypercalciuria, and kidney stones. In order to avoid adverse side effects of high serum levels of vitamin D, much effort has been made to develop vitamin D analogs that still exert the beneficial effects of vitamin D without the hypercalcemic side effects. Despite the efforts made to develop different analogs, not many, however, progressed beyond the preclinical stage [121]. Alternatively, to avoid side effects of vitamin D supplementation and to maximize the desired effectiveness, treatment locally into the lung as alternative routes of administration of vitamin D rather than peroral must be considered. Development of a drug for inhaled administration is often a common strategy to achieve high efficiency locally in the lungs and reduce side effects. However ,in the case of vitamin D, the challenge is to find a vehicle that allows effective delivery of the lipophilic agent via inhalation with improved bioavailability and sustained release of vitamin D.

In conclusion, it is important to diagnose, prevent, and treat vitamin D deficiency, since it is an epidemic all over the world, not only in patients with respiratory diseases. Vitamin D supplementation is a simple low-cost treatment that may help minimizing exacerbations in view of its immunomodulatory and anti-bacterial properties. However, efforts should be made to develop adequate strategies with vitamin D adapted for lung exacerbations rather than using existing treatment modalities with vitamin D supplementation.

Compliance with Ethical Standards

Conflict of interest Karen Maes, Jef Serré, Carolien Mathyssen, Wim Janssens and Ghislaine Gayan-Ramirez declare that they have no conflict of interest.

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