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Vitamin D and the microbiota connection: understanding its potential to improve COPD outcomes

Asmaa Ali[1,2,3*], Liang Wu[1,4*] and Sameh Samir Ali[5,6]

Abstract

The mucosa of the respiratory system is an essential site for local vitamin D synthesis, degradation, and signaling. It modulates the inflammatory and immune response by saving the integrity of the mucosal barrier and killing the invading pathogen through the induction of antimicrobial peptides. The proper functioning of the immune system within the respiratory system is influenced by the complex interactions of numerous immune pathways, including the gut-lung axis. Recent research has indicated that the gut microbiota is vital in developing and progressing chronic inflammatory chest conditions, such as asthma and chronic obstructive pulmonary disease (COPD). Furthermore, the immune-modulating function of vitamin D operates through the gut mucosa; hence, the vitamin D receptor is expressed to regulate the antimicrobial peptide. The potential protective role of vitamin D and its correlation with COPD has garnered significant interest. It is currently under exploration as a possible adjuvant therapy to aid in managing frequent exacerbation of COPD. In this review, we explored the connection between vitamin D and the immune system, as well as its relationship with microbiota. We also summarized some novel mechanisms of action of vitamin D supplementation that can impact disease exacerbation.

Keywords Vitamin D, Respiratory mucosa, COPD exacerbation, Microbiota, Preventive treatment

Introduction

Vitamin D (Cholecalciferol) is a nutritional component for good health [1]; it acts as a pleiotropic hormone, which regulates mainly the level of serum calcium, and modulates the homeostasis of phosphate, in addition to its role in bone mineralization [2]. Nearly all cell types express receptors for an active form of vitamin D (1,25 (OH) 2D), which is regulated by numerous genes [2, 3]. Consequently, vitamin D influences different body processes, including DNA repair, cell proliferation, and repair, and it is also involved in cell adhesion and apoptosis, and conversely in oxidative stress response [2, 4].

Vitamin D deficiency reflects the shortage of serum VD level and can be defined when the circulating form of VD "25 (OH)" decreases below (50 nmol/L) [5]. The bone-related diseases such as rickets and osteoporosis are reported in more than 30% of children and adults with VD deficiency [6]. Additionally, several studies

*Correspondence:
Asmaa Ali
asmaa.ali81@yahoo.com
Liang Wu
wl_ujs@163.com
[1] Department of Laboratory Medicine, School of Medicine, Jiangsu University, Zhenjiang 212013, China
[2] Department of Pulmonary Medicine, Abbassia Chest Hospital, MOH, Cairo, Egypt
[3] Department of Allergy, Al-Rashed Allergy Centre, MOH, Kuwait City, Kuwait
[4] Yizheng Hospital, Nanjing Drum Tower Hospital Group, Yizheng 210008, China
[5] Biofuels Institute, School of the Environment and Safety Engineering, Jiangsu University, Zhenjiang 212013, China
[6] Botany Department, Faculty of Science, Tanta University, Tanta 31527, Egypt

report the association between vitamin D deficiency and other diseases such as cardiovascular disease and chronic inflammatory pulmonary diseases such as cystic fibrosis, bronchiectasis, asthma, and COPD. Moreover, some immune-related diseases such as Alzheimer's disease, diabetes mellitus, and inflammatory bowel disease were linked to VD deficiency [6–9]. Despite different studies recording a significant correlation between COPD and VD deficiency, plus their inverse relationship with disease severity and exacerbation frequency, the causality link between them is still undiscovered [8–13]. Moreover, some observational studies suggested that some polymorphisms of VD receptors are associated with the development of COPD [8, 10, 11, 14]. Zosky et al. highlighted the correlation between the maternal level of vitamin D in mice and impaired lung function and structural development of offspring [15], which was an appropriate explanation; hence, the recent data showed an association between impaired lung function in early childhood and evolution of COPD later on [16]. Moreover, maternal vitamin D levels notably impact the gut microbiota, indirectly influencing the immune response in the lung through the gut-lung axis [17]. This observation highlights the crucial role that vitamin D plays in the complex and interconnected systems of the human body and emphasizes the importance of maintaining healthy levels of this essential nutrient. Additional studies in animal models investigated the effect of sub-acute and chronic exposure to cigarette smoke on mice suffering from vitamin D deficiency; the results showed a significant decrease in lung function, besides the early signs of emphysema and airway inflammation [18].

In the same way, topical application of vitamin D in the lung of elastase-induced COPD mice showed improvement in lung function through the protection of lung damage [19]. So far, in human investigations, the impact of vitamin D levels on the evolution and progression of COPD is yet unclear. However, the abovementioned observational study suggests that it is essential to be concerned about the maternal vitamin D level and connect it with the possibility of COPD development later in life. Another pathogenesis explanation was provided by Holick et al.; hence, they focus on the local level of vitamin D in airway mucosa, which is affected by exposure to the pathogen, inflammatory mediators, and inhaled toxins [6]. In the same way, in patients with COPD, the respiratory mucosa is continuously exposed to similar hazards, which lead to dysregulation of autocrine (1,25 (OH) 2D) level and VDR signaling in mucosal tissue of the respiratory tract [8, 20, 21]. Therefore, the host defense showed different forms of immune dysregulation, including abnormal secretion of protective molecules, alteration of the epithelial barrier and its protective function, and significant changes in the microbiota composition [20, 21]. A sufficient level of vitamin D may protect these dysregulated processes in several ways as maintaining the integrity of the mucosal barrier, promoting the killing of pathogens through induction of the antimicrobial peptide (AMP), and modulation both innate and adaptive immune responses [7, 22, 23].

In this narrative review, we discussed the relationship between COPD pathogenesis and vitamin D deficiency, focusing on the influence of gut microbiota and the potential of vitamin D supplementation to mitigate the frequency of COPD exacerbations.

Vitamin D metabolism

In healthy condition

The primary source of vitamin D is animal or plant-based food; however, it can be synthesized in the skin by UVR radiation [24]. The inactive form of vitamin D enters the circulation after binding with a specific protein (VDBP). It reaches mainly the liver, where it is converted to another inactive form of vitamin D (25 (OH) D) by a specific enzyme, which is expressed in liver cells (CYP2RI and CYP27A1) [25]. However, several studies reported that mucosal epithelial cells of the respiratory tract and intestine, as well as monocyte and macrophage cells, expressed the vitamin D converting enzyme, too [24–27]. 25 (OH) D needs to be activated by CYP27B1 enzyme, which is expressed in the kidney as well as in other cells such as epithelia and immune cells, to finally active form (1, 25 (OH)2 D) [27–30] (Fig. 1). In addition, the hormone 1,25 (OH) 2D can regulate the expression of multiple genes by binding with the vitamin D receptor (VDR). This receptor is expressed predominantly in the gastrointestinal system, especially the intestinal enterocytes and pancreatic islets, and it is moderately found on the distal renal tubules and osteoblasts. However, it is also present at lower levels in numerous other tissues and various epithelial and immune cells [31–33]. 1,25(OH)2D regulates the expression of VDR; the later also is regulated by other factors such as FGF-23 and PTH [34]. The primary function of 1,25-(OH) 2 D is to ensure an adequate amount of calcium and phosphorus in the bloodstream. This hormone plays a crucial role in regulating the absorption of these essential minerals in the body, which is crucial for maintaining strong bones and teeth, proper muscle function, and overall health. Without sufficient levels of 1,25-(OH) 2 D, the body may struggle to maintain the necessary levels of calcium and phosphorus, which can lead to a range of health problems and complications. If blood calcium levels decrease, 1,25-(OH) 2 D will engage with VDR in osteoclasts to trigger bone resorption and elevate calcium and phosphorus levels [35]. However, the effects of vitamin D extend beyond its role in regulating

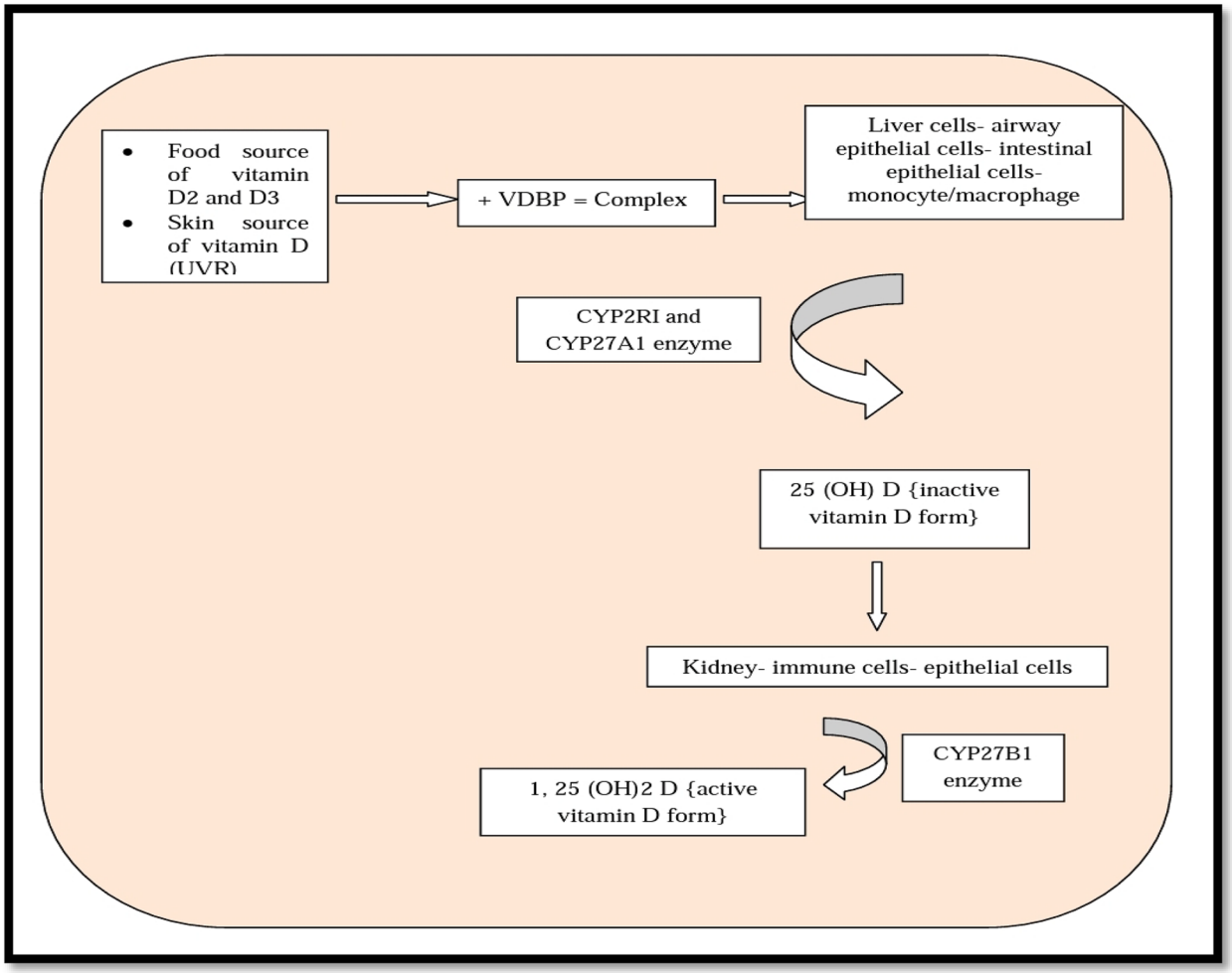

Fig. 1 Pathway of vitamin D metabolism. VDBP: vitamin D binding protein, CYP2RI, CYP27A1, CYP27B1: Vitamin D 25 hydroxilase enzyme

calcium and phosphorus levels and promoting healthy bone development since other extra-renal cells, such as some immune cells and airway epithelial cells, contain the vitamin D receptor (VDR) and have the ability to convert 25-hydroxyvitamin D (25(OH)D)—the inactive form of vitamin D—into its active metabolite, 1,25-dihydroxy vitamin D (1,25(OH)2D). Therefore, vitamin D can affect various physiological processes beyond bone health. The immune function of vitamin D was recorded in different research, and it is considered a neurohormone or even a cytokines-like component with multiple immunological functions. Vitamin D induces its function by enhancing the innate immune response and promoting the production of different immunological cells as neutrophils and monocytes, in addition to facilitating its proliferation and function [2, 32, 33]. Moreover, the immunological functions of vitamin D extend to modulating the cellular immune response in the respiratory system. Vitamin D is a diverter of the inflammation pathway; it can inhibit type I inflammation and switch the direction toward type II inflammation. Hence vitamin D arouses Th2 cells and speculates the production of its cytokines cocktail as IL-1 and TNF-α while suppressing the other inflammatory cytokines as IL-10 and IL-4, in addition to modulating the regulatory function of IL-17 by self-tolerance mechanisms [25, 31].

In inflammatory airway disease

Airways in patients with chronic lung disease showed chronic inflammation and impaired defense, increasing susceptibility to repeated infection. In addition to exposure to air pollutants and cigarette smoke, that is involved in disease pathogenesis [36–38]. Studies showed that airway epithelial cells are associated with impaired 1,25(OH)2D synthesis after viral and bacterial infections. Hence, the expression of catabolic enzymes CYP24A1 and CYP27B1 increased after infection in airway epithelium, and thereby conversion of 25(OH) D into

1,25(OH)2 D, the active metabolite [29, 39, 40]. On the other hand, some studies explain the impaired local vitamin D level by exposure to proinflammatory mediators, which affect the expression of both VDR and CYP27B1 enzymes in epithelial cells [30, 41]. However, the opposite condition happened in immune cells (neutrophil, monocyte, and macrophage) [42–44]. Therefore, it has been observed that administering 25(OH)D to immune cells results in an escalation of antimicrobial responses. This observation could serve as an additional defense mechanism to compensate for the augmented degradation of 25(OH)D and 1,25(OH)2D in the epithelial layer during inflammation. Such a response is crucial in mitigating the effects of inflammation and enhancing the body's immunity against microbial pathogens. Furthermore, two recently conducted studies have delved into the consequences of inhaling toxins on the levels of 1,25(OH)2D and the responsiveness of immune cells. The initial study discovered that the expression of VDR increased but did not significantly affect the response of VD [45]. While in the second one, the expression of the CYP2A1 enzyme was induced [46].

The data were limited when considering the consequence of chronic inflammatory status in lung tissue of patients with chronic lung disease in correlation with vitamin D metabolism and responsiveness; hence, only one animal bleomycin fibrosis model showed that TGF-b1 diminished the VDR expression, which might support the hypothesis [47]. However, this data is still inadequate to clarify that the disease-associated factors could be implicated in the lack of VD level in some way or another, plus what is the role of other immune cells and epithelial and mesenchymal cells in modifying the action of VD in the experimental situation?

Vitamin D deficiency and COPD

Chronic obstructive lung disease is a non-curable disease and is considered the most common chronic and systemic inflammatory disorder. It is characterized by progressive irreversible limitation of airflow in respiratory airways. The main etiological factors were smoking and different environmental pollution, in addition to associated genetic predisposition. In chronic lung disease, vitamin D insufficiency and deficiency are markedly recorded; however, the underlying mechanism of this link was not fully understood. The experimental animal models showed some promising results, in which VD supplementation enhanced surfactant synthesis and type II alveolar cell synthesis. Moreover, VD positively affected the proliferation of fibroblasts and the process of alveolarization [48].

A recent review emphasizes the importance of measuring vitamin D levels in patients with COPD, as studies have found a correlation between low levels and impaired lung function. Adequate intake of vitamin D may have benefits beyond preventing bone fractures. Factors such as inadequate food intake, aging, lack of sun exposure, medication use, and health issues can contribute to vitamin D deficiency [49, 50].

From a genetic and immunologic perspective, a recent study delves into the potential causal link between vitamin D and chronic obstructive pulmonary disease (COPD) development. Research indicates that the Th1 immune response and Th17 cells are implicated in COPD and may contribute to a connection between vitamin D deficiency and the disease. Furthermore, lacking this vitamin may exacerbate inflammation and promote parenchymal degradation by producing chemokines (via NF-ƘB) and Matrix Metalloproteinase (MMP)-9. In addition to affecting the production of IL-18 and TNF-a, it directly influences corticosteroid resistance and histone acetylation [49]. Additionally, Pfeffer et al. and Banerjee et al. discovered that vitamin D is critical in regulating smooth muscle remodeling [51, 52].

Considering the calcemic effect of VD and the pathogenesis of COPD, research findings indicate a noteworthy connection between airflow limitation and heightened odds ratios (OR) for osteoporosis (OR 1.9). This association becomes even more pronounced in cases of severe airflow obstruction, where the OR escalates to 2.4. Importantly, this pattern holds across both genders. The implications drawn from the study underscore the importance of actively addressing osteoporosis in individuals with moderate to severe COPD [53].

In another study, almost half of the patients, regardless of gender, had osteoporosis or osteopenia [54]. The prevalence of osteoporosis varies between 8.7 and 69% with higher rates observed in patients with chronic illnesses or exacerbations. COPD patients are particularly prone to vertebral fractures, with reported incidence rates of 24 to 79% [55]. Osteoporosis can be linked to various aspects of lung function. Moreover, a comparative investigation encompassing COPD patients with and without osteoporosis revealed notable disparities. Those who have osteoporosis exhibited marked reduced BMI and elevated residual volume (RV) expressed as a percentage of total lung capacity (RV%TLC) [56]. Furthermore, in COPD, osteoporosis can arise due to a convergence of factors leading to vitamin D deficiency and subsequent bone resorption. Individuals with COPD often skew older, exhibit reduced physical activity, are more confined to their homes, and possess diminished muscle mass, all of which contribute to lower vitamin D synthesis. Given that vitamin D deficiency is a crucial driver of osteoporosis, proactive assessment of

its levels is imperative in COPD cases. For patients found to be deficient, including replacement therapy warrants consideration [49].

Concerning the non-calcemic effects of vitamin D, substantial studies have highlighted its antibacterial and mycobacterium-related impacts, in addition to its antiviral properties, mediated through diverse mechanisms. Antimicrobial polypeptides, like cathelicidin, are under the genetic control of vitamin D response elements (VDREs) within their promoters. Cathelicidin, with its efficacy against mycobacteria and various antibiotic-resistant strains such as Pseudomonas aeruginosa and Staphylococcus aureus, as well as different viruses and chlamydia, assumes a pivotal role. These actions bear significant importance due to their influence on the progression of COPD, where infectious exacerbations play a crucial role [49, 51, 52]. Furthermore, many human studies have underscored the clinical link between vitamin D deficiency and respiratory infections. For instance, in an investigation involving 800 healthy males, individuals with serum 25(OH) D concentrations below 40 nmol/L exhibited a notably higher number of days of absence from duty attributed to respiratory infections [57]. Similarly, a more comprehensive study encompassing 2135 patients, who assessed VD levels before hospitalization, revealed that those with vitamin D levels lower than (10 ng/mL) had a 2.33-fold increase in hospital-acquired bloodstream infections [58]. Data also exists concerning the correlation between viral infection and vitamin D deficiency. Both circumstances exhibit a higher prevalence during winter, and addressing vitamin D deficiency could enhance the prognosis of respiratory infections [59]. In a separate randomized controlled trial involving 5292 patients, participants were administered either a placebo or 800 IU of vitamin D. Although there was a trend towards reduced reported infections and antibiotic usage, this trend did not reach statistical significance [60]. Accumulated data propose that vitamin D might be linked to recurrent exacerbations, colonization, and bacterial eradication [49, 51, 52]. In a study initially designed to explore the impact of daily azithromycin on COPD exacerbations, Kunisaki et al. observed no significant correlation between VD levels and either the occurrence of the first exacerbation or the frequency of exacerbations. It is worth noting, however, that vitamin D insufficiency was identified in just 33% of the patient cohort [61]. The researchers conducted an extensive study involving 97 patients suffering from COPD. The study's primary objective was to explore and establish potential correlations between factors, including vitamin D levels, VDR polymorphism, exacerbations, human rhinovirus (HRV) susceptibility, and outdoor activity. In doing so, the researchers aimed to understand better the complex interplay between these factors and their impact on COPD patients. According to the study's findings, low levels of 25-hydroxyvitamin D do not correlate with the frequency of exacerbations or susceptibility to HRV-related exacerbations in patients suffering from COPD. Nevertheless, it is worth noting that patients who usually spend less time outdoors are likely to have lower concentrations of 25-hydroxyvitamin D, regardless of the duration of the day [62]. In another comprehensive study centered on chronic obstructive pulmonary disease (COPD) exacerbation, it was discovered that the initial vitamin D level significantly correlated with pulmonary function tests, the severity of dyspnea, and the duration of hospital stay. This observation suggests that maintaining adequate vitamin D levels may help COPD patients mitigate exacerbations' effects. However, the study found no significant relationship between the initial vitamin D level and the number of exacerbations experienced in the previous year, indicating that other factors may play a more decisive role in determining the frequency of COPD exacerbations [63]. Furthermore, a study conducted over an extended period found that a significant proportion of Chronic Obstructive Pulmonary Disease (COPD) patients who received primary care exhibited a deficiency in vitamin D, specifically; the study found that 77% of these patients lacked sufficient amounts of this vital nutrient. Nevertheless, no discernible differences were observed in terms of exacerbation rates and mortality after factoring in the impact of vitamin D supplementation and categorizing patients based on their vitamin D levels. These findings suggest that vitamin D deficiency is common among COPD patients but may not necessarily contribute to their symptoms or overall health outcomes [64]. Nevertheless, a more recent study tracking 426 COPD patients for 3 years did not unveil a noteworthy correlation between VD levels and the incidence of COPD exacerbations or mortality rates [14]. An Italian study involving 97 COPD patients revealed a connection between vitamin D deficiency and a higher occurrence of frequent exacerbations along with repeated hospitalizations [65]. A recent meta-analysis of patients suffering from exacerbations has shown that their vitamin D levels were lower than stable individuals. However, it must be noted that there is no conclusive evidence that directly links vitamin D deficiency to an increased risk of COPD exacerbation. While the current data does suggest a correlation between vitamin D levels and exacerbations, it does not provide definitive proof of a direct link between the two [8]. Therefore, further research is required to establish a clear connection between vitamin D deficiency and COPD exacerbation.

Vitamin D and microbiota

Vitamin D classically regulates gene transcription through vitamin D receptors (VDR). It plays multiple immunological roles by inhibiting Th17 and Th1 responses, impairing the development and function of B cells, promoting Tregs function, and stimulating antimicrobial peptides from immune cells [66].

Recent studies reported that VD level is directly connected with changes in microbiota composition [67, 68]. Furthermore, animal studies found that dietary restriction of VD in mice promotes the increase of Bacteriodetes and Proteobacteria phyla in gut composition [68, 69]. Additionally, in a large human study, a significant link has been found between two VDR polymorphisms and microbiota variation in some inflammatory diseases [70]; hence, the genus *Parabacterioides* (phylum: Bacterioidetes) became more abundant. Another supportive study recorded that repeated ingestion of VD supplementation to healthy subjects enhances the enrichment of *Prevotella* and *Bacteroides*, which belong to the Bacteroidetes phylum [71].

In a contrary study, excess VD intake promotes Prevotella abundance and decreases *Haemophilus* and *Veillonella* (Proteobacteria and Firmicutes, phylum, respectively) [67]. Unexpectedly, data about the direct effect of VD on bacteria still needs to be improved; future in vitro studies are recommended to uncover a possible anti-bacterial action of VD.

Role of vitamin D in the treatment of COPD

Vitamin D has been shown to play a crucial role in host defense mechanisms, particularly in chronic inflammatory lung conditions. However, it is not uncommon for individuals with such conditions to exhibit a deficiency in this essential nutrient. Consequently, there is a growing interest in exploring strategies aimed at boosting local 1,25 (OH) 2D levels or utilizing vitamin D as a potential treatment option. To this end, clinical and animal studies have been conducted to investigate the impact of vitamin D supplementation on chronic airway diseases. These studies provide valuable insights into the potential benefits of using vitamin D as a therapeutic agent for such conditions.

Impact on the response of inhaled steroid therapy

Inhaled corticosteroids (ICS) are the primary treatment for patients with COPD and asthma, sometimes combined with long-acting bronchodilators. However, the effectiveness of corticosteroid therapy varies among patients, particularly those with steroid-resistant (SR) asthma. The reasons behind this resistance are multifaceted and encompass factors such as genetic predisposition, impaired glucocorticoid receptor binding, inflammation driven by T helper type 17 cells (Th17), oxidative stress, and reduced numbers of interleukin-10-secreting regulatory T cells (Tregs) that typically mitigate the Th17-driven inflammation cascade [72].

A study has demonstrated that 1,25(OH)2D can reverse steroid resistance by fostering the ex vivo production of IL-10-secreting Tregs. When applied, vitamin D reinstates corticosteroid sensitivity in CD4+ T cells sourced from individuals with SR-asthma [73]. Furthermore, research indicates that administering vitamin D to asthmatic patients with low serum vitamin D levels could enhance their responsiveness to steroids. This therapeutic approach holds promise for countering oxidative stress and alleviating Th17-mediated inflammatory reactions [74–79].

Nevertheless, the corticosteroid dexamethasone has been demonstrated to elevate the expression of the 25(OH)D and 1,25(OH)2D-degrading enzyme CYP24A1 in renal cells and osteoblasts. This observation points to a two-way interaction between corticosteroids and 1,25(OH)2D, which may curtail 1,25(OH)2D levels for patients [80]. Further investigations are imperative to ascertain whether vitamin D can enhance corticosteroid responsiveness in COPD.

COPD exacerbation and role of vitamin D

COPD patients face a significant burden from exacerbations which can lead to a faster decline in lung function and more frequent hospital admissions [81]. Pollutants, bacterial, viral infections, or a combination of all three can trigger these exacerbations [82, 83]. According to research findings, individuals with Chronic Obstructive Pulmonary Disease (COPD) tend to have lower levels of serum 25-hydroxyvitamin D, commonly referred to as 25(OH) D, compared to control groups matched in age and smoking. This deficiency in vitamin D has been closely associated with the likelihood of experiencing more severe exacerbations of the disease. Studies have shown this is a significant risk factor for COPD patients, with a higher prevalence of exacerbations and increased hospital admissions [8–10]. Therefore, maintaining adequate levels of vitamin D is crucial in managing the progression of the disease. Bacterial infections significantly cause COPD exacerbations, accounting for 50% of all cases. Advances in study design and sampling techniques have allowed for a better understanding of bacteria's role in causing these exacerbations. New techniques using 16S rRNA sequencing have shown that certain bacterial strains become more abundant during exacerbations, with the Proteobacteria phylum being particularly prevalent [83, 84].

A recent study revealed that 1,25(OH)2D can enhance the defensive capability of airway epithelial cells against

bacterial threats. Upon treatment with 25(OH)D and 1,25(OH)2D, airway epithelial cells exhibit heightened expression of hCAP18/LL-37, thus fortifying their ability to counter NTHi, a specific Gram-negative bacterium often linked to COPD exacerbations [85, 86]. Moreover, the administration of 1,25(OH)2D not only amplifies the expression of the antimicrobial peptide (AMP) hCAP18/LL-37 but also demonstrates efficacy in eliminating both Pseudomonas aeruginosa and Bordetella bronchiseptica, both of which are Gram-negative bacteria [86]. These observed antibacterial effects of 1,25(OH)2D on airway epithelial cells in vitro have recently received corroboration in vivo through the work of Vargas Buonfiglio et al. Their research showcased that vitamin D supplementation heightens antimicrobial activity against the Gram-positive bacterium Staphylococcus aureus within healthy non-smokers' airway surface liquid (ASL). Notably, this effect is contingent upon the presence of hCAP18/LL-37 [87].

However, according to a separate animal study conducted on the airway, the results obtained were quite different. Specifically, the study found no significant influence of 1,25 (OH) 2D on Defb4 or mCramp (practically the murine equivalent of CAMP) expression [88]. This particular outcome could be attributed to the lack of vitamin D response elements (VDREs) in the promotors of mCramp and Defb4. As a result, this suggests that mice may not be the most optimal models for investigating the impact of 1,25(OH)2D on AMP-mediated host defense during infections [89]. Therefore, it is necessary to consider other animal models that may be more appropriate for investigating this particular aspect of host defense.

Recent scientific research conducted on mice has revealed that the application of topical vitamin D3 treatment can lead to an increase in CAMP expression [90]. This finding, in turn, has demonstrated antibacterial effects on skin mucosa. However, it is essential to note that there is currently no conclusive correlation between vitamin D levels and the occurrence of pulmonary infections caused by Streptococcus pneumoniae or Pseudomonas aeruginosa in murine studies. Nevertheless, findings from other studies conducted on mice have shown that vitamin D can offer protection against gut bacterial infections. This result suggests that vitamin D's antibacterial effects are likely modulated through various mechanisms, including enhancing epithelial barrier integrity [91, 92].

Collectively, these observations highlight the capacity of 1,25(OH)2D to bolster defense mechanisms and enhance the clearance of bacterial infections, while simultaneously tempering exaggerated immune responses. These attributes potentially provide insights into the link between vitamin D deficiency and the exacerbation of COPD.

Exceeding the abovementioned observations about the mechanisms by which VD could play a role in minimizing COPD exacerbation, either through its immune modulation effects or with its newly discovered antibacterial action, Table 1 summarizes human observational studies and randomized control trials on the link between VD deficiency and COPD exacerbation, as well as the potential impact of VD intake in reducing the rate of exacerbation. Although there have been conflicting results regarding the effectiveness of using VD supplementation as an add-on therapy to reduce COPD exacerbation rates, all studies agree that measuring the level of VD in the serum of all COPD patients is crucial [93–110]. Additionally, many studies suggest conducting further research to determine the effects of subgroup classification or varying VD supplementation doses [93, 106, 108, 109].

Vitamin D supplementation effect on microbiota

Various studies have contributed to understanding antimicrobial peptides' (AMPs) role in governing the configuration of the gut microbiota. Notably, investigations have highlighted the potential influence of Paneth cell-derived defensins in shaping the microbiome's structure [111]. This concept gains further validation through the observation that numerous commensal gut bacteria benefit from AMP protection, including examples like the 1,25(OH)2D-inducible hCAP18/LL-37 and hBD-2, whereas pathogens tend to exhibit heightened sensitivity [85]. Certain gastrointestinal conditions, like inflammatory bowel disease (IBD), have been associated with shifts in gut microbiota composition. Likewise, conditions that impact the respiratory system, such as COPD and asthma, are also implicated in this dynamic relationship, emphasizing the crucial role played by the so-called gut-lung axis [112, 113].

The complex interplay between gut microbiota and lung health involves various mechanisms. One such mechanism is the production of short-chain fatty acids (SCFAs) that have a broad range of effects on immune and structural cells. SCFAs produced in the intestinal environment can directly impact lung immunity. This impact is partly attributed to their ability to influence myeloid cells within the bone marrow, which migrate to the airways and modulate local immune responses. Therefore, SCFAs serve as crucial mediators in the communication between the gut microbiota and the lung, highlighting the importance of maintaining a healthy gut microbiome for optimal lung function [114].

The microbiota landscape is a complex ecosystem that boasts diverse microbial species, each contributing to

Table 1 Association between VD deficiency and COPD exacerbation

Study year	Study type	Objectives	Findings	Recommendations
Rafiq et al. 2022 [93]	Multicenter, double-blind, randomized controlled trial.	Study the effect of vitamin D supplementation on exacerbation frequency in COPD patients with vitamin D deficiency and focus on exacerbation rate, time to first and second exacerbations, hospitalizations, use of antibiotics and corticosteroids, pulmonary function, respiratory mouth pressure, physical performance, skeletal muscle strength, inflammatory markers, nasal microbiota composition, and quality of life.	Vitamin D supplementation did not reduce the exacerbation rate in COPD patients with a vitamin D deficiency, with no significant differences regarding time to first and second exacerbations, hospitalizations, use of antibiotics and corticosteroids, pulmonary function, respiratory mouth pressure, physical performance, skeletal muscle strength, inflammatory markers, nasal microbiota composition, and quality of life between the intervention and placebo groups.	The study suggested that vitamin D supplementation may not effectively reduce exacerbation rates in COPD patients with a vitamin D deficiency. Further research may be needed to confirm these findings and to determine the optimal treatment for COPD patients with vitamin D deficiency.
Soeroto et al. 2021 [94]	Cross-sectional.	Investigate how vitamin D levels impact FEV1, exacerbation frequency, and symptom severity, as evaluated by the COPD assessment test (CAT), in individuals with stable COPD.	Low vitamin D levels are associated with more frequent exacerbations and higher CAT scores in stable COPD patients but are not associated with FEV1 (%) predicted.	Assessing the level of VD in patients with stable COPD is crucial. It is advisable to conduct additional research on the connection between COPD and VD.
Jorde et al. 2021 [95]	Cross-sectional.	Explore the potential connection between COPD and serum vitamin D levels and investigate whether low 25-OHD levels impact COPD symptoms, inflammation, exacerbations, and lung function.	COPD patients often have vitamin D deficiency, and 25-OHD levels are linked to inflammation, severity, and disease progression. Serum 25-OHD is slightly connected to FEV1 and varies among COPD patients; it has weak negative correlations with annual FEV1 change, C-reactive protein, and interleukin-6.	The research paper sheds light on the correlation between serum 25-OHD levels and COPD, which can assist in developing new treatment approaches for COPD patients.
Lokesh et al. 2021 [96]	Case-control study	Investigate the relationship between vitamin D deficiency and COPD in a rural population in South India. It examined the serum levels of 25-OH-vitamin-D in COPD patients and matched individuals from the MUDHRA cohort, as well as risk factors contributing to deficiency. Moreover, it determined the optimal vitamin D levels for COPD and AECOPD.	In South India, over 60% of people with COPD lacked vitamin D, even with sunlight exposure. Those with a deficiency were three times more likely to have exacerbations. Low Vitamin D levels were linked to both COPD and AECOPD.	It is recommended that people with COPD get tested for vitamin D deficiency and receive appropriate treatment. Research shows that maintaining sufficient levels of vitamin D may lower the likelihood of COPD exacerbations. However, more studies are necessary to establish the ideal amount of vitamin D supplementation for individuals with COPD.
Pandey et al. 2021 [97]	Case-control.	To understand how inflammation and imbalances in antioxidants and oxidants contribute to COPD. Researchers will measure levels of vitamin D, C-reactive protein (CRP), superoxide dismutase (SOD), catalase, and malondialdehyde (MDA) in both COPD patients and healthy individuals.	COPD patients have an imbalance between oxidants and antioxidants, a vitamin D deficiency, lower SOD and Catalase levels, and higher MDA and CRP levels than healthy individuals.	The study recommends that a biomarker-based study testing the efficacy of novel antioxidants or other agents will help modify the course of COPD. The study suggests further research to determine the effectiveness of novel antioxidants or other agents as VD supplementation in treating COPD.

Table 1 (continued)

Study year	Study type	Objectives	Findings	Recommendations
Ghosh et al. 2020 [98]	Cohort study.	To study the link between vitamin D levels and respiratory symptoms in smokers with and without COPD and to see if low vitamin D levels lead to poorer respiratory outcomes.	Vitamin D deficiency is associated with increased respiratory symptoms, decreased functional status, increased frequency of severe exacerbations, and airway wall thickening on chest CT scans in current and former smokers with and without COPD. Vitamin D deficiency was associated with worse quality of life, increased dyspnea, and decreased exercise tolerance.	The study recommends more research identifying how vitamin D supplementation can enhance disease outcomes. Future studies could explore the impact of vitamin D metabolism on COPD development, its various phenotypes, and its role in preventing COPD exacerbations.
Burkes et al. 2020 [99]	Cross-sectional.	To investigate the link between 25-OH-vitamin D levels and COPD outcomes, such as lung function and exacerbations. It may also identify vitamin D levels as a marker for adverse COPD-related outcomes.	21% of the SPIROMICS cohorts have insufficient levels of vitamin D, mainly young, active smokers and black individuals. This deficiency has been associated with reduced lung function, a higher risk of COPD exacerbation, and unfavorable outcomes. A drop of 10 ng/mL in 25-OH-vitamin D can serve as an indicator of poor COPD-related results.	The study recommended monitoring the level of VD in COPD patients and commenced vitamin D supplementation to improve COPD-related outcomes. However, it is essential to note that further research is needed to determine the optimal dose and duration of vitamin D supplementation in this population.
Köktürk et al. 2020 [100]	Cross-sectional.	To measure vitamin D deficiency in COPD patients and its link to exacerbation and mortality.	Many COPD patients in Turkey have severe vitamin D deficiency, but it does not affect their survival or the likelihood of exacerbation. Vitamin D levels are not linked with exacerbation frequency, microorganism growth, hospital stay length, FEV1, or survival rates.	It suggests that carefully designed randomized controlled studies are needed to clarify the issues related to the effect of vitamin D supplementation in preventing COPD exacerbations.
Li et al. 2020 [101]	Systematic review and meta-analysis of RCT	This study analyzes different RCTs to measure the effectiveness of vitamin D therapy on patients with COPD. It evaluates the impact on lung function, exacerbations, sputum volume, 6-min walk distance, and COPD assessment test score.	After analyzing 25 articles with 2670 participants, the study concluded that vitamin D therapy had a significant positive effect on lung function (FEV1, FEV1/FVC), 6-min walk distance, and reduced acute exacerbation, sputum volume, and COPD assessment test score.	The study suggests that vitamin D therapy could be a potential treatment option for improving lung function and reducing exacerbations in patients with COPD. Further research is needed to determine the optimal dosage and duration of vitamin D therapy for COPD patients.
Jolliffe et al. 2019 [102]	Systematic review and meta-analysis of RCT	To review data from past trials on vitamin D's impact on COPD, look for variations in results, and see if it reduces exacerbations in patients with low VD levels.	Vitamin D supplementation did not influence the overall rate of moderate/severe COPD exacerbations. However, vitamin D supplementation safely and substantially reduced the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels.	The study suggests that vitamin D supplementation may be beneficial in reducing the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels. Further research is needed to confirm these findings and to determine the optimal dose and duration of vitamin D supplementation for COPD patients.

Table 1 (continued)

Study year	Study type	Objectives	Findings	Recommendations
Mishra et al. 2019 [103]	Case-control	A study compared vitamin D levels in COPD patients and healthy individuals and examined the relationship between vitamin D levels and lung function.	Low vitamin D levels are linked to lower lung function, especially in COPD patients. This effect is more potent in COPD patients, and their expiratory airflow limitation worsens. COPD patients also have lower predicted postbronchodilator FEV1% severity than healthy volunteers.	The study recommended regularly checking vitamin D levels to prevent the negative impact on lung function. However, further research is needed to validate this connection, specifically in India.
Ferrari et al. 2018 [104]	Review and meta-analysis	The literature review investigates the relationship between vitamin D and COPD exacerbation. It analyzes data on a diet, 25(OH)D, and polymorphism to identify the best vitamin D marker, patient groups that may benefit, and safe supplement dosages.	The relationship between how often COPD patients experience exacerbations and their vitamin D levels is still debated in observational studies. However, a meta-analysis has found a negative connection between serum vitamin D and exacerbations. Additionally, two clinical trials have shown that vitamin D3 supplementation can lower the risk of moderate and severe exacerbations in COPD patients. It is worth noting that a patient's susceptibility to exacerbations may be affected by their vitamin D binding protein (VDBP) polymorphisms.	Supplementing with vitamin D may help prevent the worsening of COPD in patients with low levels of the vitamin. However, more research is necessary to determine the most helpful marker for vitamin D, which subgroups of patients will benefit from, and the appropriate dosage of supplements to avoid toxicity.
Khan et al. 2017 [105]	Randomized controlled trial.	To assess whether vitamin D supplementation can decrease the frequency of acute exacerbations in individuals with Chronic Obstructive Pulmonary Disease (COPD).	Vitamin D supplements reduced acute exacerbations in COPD patients. 25(OH) levels increased from 24.08 ± 2.58 to 29.60 ± 8.74 after 6 months. FVC increased from 77.83 ± 5.49 to 91.34 ± 5.52. Only four patients (3.3%) had exacerbations after 6 months.	The study recommends that vitamin D supplementation be considered a potential intervention to reduce the number of acute exacerbations in COPD patients. However, further studies are needed to confirm the effectiveness of vitamin D supplementation in COPD patients. It is also important to note that vitamin D supplementation should be given for a prolonged period and monitored to avoid exceeding the optimum vitamin D level in the blood.
Rafiq et al. 2017 [106]	Randomized, double-blind, placebo-controlled pilot trial.	To investigate the effects of vitamin D supplementation on COPD patients with a deficiency in vitamin D and how it affects respiratory muscle strength, physical performance, pulmonary function, handgrip strength, exacerbation rate, and quality of life.	Adding vitamin D supplements did not improve respiratory muscle strength or physical performance in COPD patients who lacked vitamin D. Despite increased serum 25(OH)D levels after 6 months, there were no significant differences in primary outcomes compared to the placebo group.	The study recommended that more studies are needed to determine if higher doses of vitamin D supplements can improve muscle function and slow the progression of COPD.

Table 1 (continued)

Study year	Study type	Objectives	Findings	Recommendations
Park et al. 2016 [107]	Cross-sectional	To examine the possible link between vitamin D levels and GC polymorphisms with clinical outcomes in COPD patients.	The study found that vitamin D status and GC polymorphisms were associated with airway obstruction, exercise capacity, and emphysema severity but not disease exacerbation.	The study recommended that more research is needed to understand the correlation between GC polymorphisms and vitamin D deficiency in diverse patients.
Zendedel et al. 2015 [108]	Double-blind placebo-controlled randomized clinical trial.	To evaluate the effects of vitamin D intake on COPD exacerbation and FEV1 in patients with severe and very severe COPD.	Vitamin D intake decreased COPD exacerbation in patients with severe and very severe COPD. Vitamin D intake improved FEV1 in patients with severe and very severe COPD. There were significant differences in FEV1 and the number of COPD exacerbations between the case and control group patients after the intervention. The case group showed a significant increase in FEV1 and a significant decrease in the number of COPD exacerbations after the study.	It is suggested that baseline serum vitamin D levels should be recorded in similar studies, and the effect of vitamin D intake should be evaluated regarding the baseline serum vitamin D levels.
Martineau et al. 2015 [109]	Multicentre, double-blind, randomized controlled trial.	The study investigates if vitamin D3 supplements reduce moderate to severe COPD exacerbations and respiratory infections, with consideration of patients' initial vitamin D levels.	Vitamin D3 supplementation did not affect the time to first moderate or severe exacerbation or upper respiratory infection compared to placebo. However, a 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.	The study recommended that vitamin D3 supplementation be considered for patients with COPD with a baseline serum 25-hydroxyvitamin D concentration of less than (50 nmol/L) to reduce the risk of moderate or severe exacerbation. However, further research is needed to determine the optimal dose and duration of vitamin D3 supplementation for patients with COPD.

its richness and vibrancy. Within this landscape, certain species are exceptionally skilled at producing short-chain fatty acids (SCFAs), which have been shown to impact overall health positively. This concept is just one aspect of the intricate web of interactions that make up the microbiota, and understanding these dynamics is crucial in unlocking the full potential of this fascinating world [115].

Notably, strong evidence underscores the significant influence of vitamin D deficiency and supplementation on the makeup of the adult and infant gut microbiota, particularly in various diseases [115–117]. Nevertheless, due to the current limitations encompassing the number of randomized controlled trials (RCTs) and the relatively small sample sizes, the exact ramifications on the microbiota and the precise mechanisms involved remain to be fully elucidated [115].

However, in a recent review, Bellerba et al. explored the relationship between vitamin D and changes in human gastrointestinal microbiota. This connection is vital because gut microbiota has been linked to various diseases. The review analyzed 25 studies involving human participants investigating the association between gut microbiota and vitamin D. These included examining the effects of vitamin D supplementation, dietary intake of vitamin D, and levels of 25(OH)D. While the studies were diverse and had some limitations, the authors suggest that more research should be conducted using well-designed animal-based studies or extensive randomized controlled trials (RCTs) to understand better the role of vitamin D in modulating the gastrointestinal microbiota [118]. The same author conducted an RCT, which included 60 patients with colorectal cancer to evaluate the effects of VitD supplementation on gut microbiota. It was found that supplementation may impact the microbiota, and this effect may be partially mediated by 25(OH)D. The study also revealed the importance of including sex/gender as a variable in microbiome studies, as differences were observed between male and female participants [119].

Furthermore, another RCT examined the effect of VD3 supplementation in patients with metastatic colorectal cancer; results suggest that vitamin D may fight colorectal cancer. Hence, encouraging results have been seen in a phase 2 trial. However, more research is needed as the evidence examined is preclinical and epidemiological and only reports on current clinical trials [120].

Ongoing research on the effects of vitamin D (VD) on the immune system concerning different diseases has led to promising findings that suggest supplementing with VD could be crucial in supporting a healthy diversity of gut microbiota and strengthening the immune response of beneficial microbiota strains in patients with systemic inflammatory conditions like COPD. This result is because VD has been found to play an important role in regulating immune function, including the proliferation and differentiation of immune cells and the production of inflammatory cytokines. Supplementing with VD may help to restore immune balance and reduce inflammation in patients with COPD, which could have far-reaching benefits for their overall health and well-being. Recent studies have identified notable alterations in the lung microbiome composition of individuals diagnosed with chronic obstructive pulmonary disease (COPD) and asthma. Specifically, these changes have been attributed to the crucial immunological role of vitamin D (VD) in maintaining lung commensal. These findings suggest that the modulation of the lung microbiome through regulating VD levels may hold promise as a therapeutic strategy for managing these respiratory conditions [121]. Various factors such as environmental exposures, infections, airway remodeling, and antibiotic treatments can cause changes in the airway epithelial barrier. These changes can trigger immune responses and lead to further microbiome changes, worsening with disease progression [121, 122].

Two studies suggest that vitamin D may affect the airway microbiome. Toivonen et al. found a correlation between low vitamin D levels and decreased nasopharyngeal microbiota, with more severe bronchiolitis symptoms [123]. The second study examined the impact of vitamin D supplementation on the presence of Staphylococcus aureus, Staphylococcus epidermidis, and Corynebacterium species in the sputum of cystic fibrosis (CF) patients. It found differences in abundance between vitamin D-deficient and sufficient CF patients [124].

A recent review has summarized the current knowledge regarding the interaction between vitamin D, the lung microbiome, and chronic lung diseases like tuberculosis. The study proposes how these factors could affect the outcome of tuberculous granuloma and explains the underlying drivers of MTB infection outcomes within these structures. The authors suggest that potential therapeutic strategies could aim to redirect the outcome of tuberculosis by balancing vitamin D, the lung microbiome, and the tuberculous granuloma. However, the study does not provide specific recommendations for treating or preventing tuberculosis [125].

At that point, research indicates that alterations in microbiota could contribute to the development of chronic respiratory illnesses, and vitamin D deficiency and supplementation may also be factors. Nonetheless, additional research is necessary since the existing evidence is founded on several randomized controlled trials with limited sample sizes.

Conclusion and future prospect

The causes of COPD include chronic exposure to cigarette smoke and air pollution, as well as harmful substances like proteolytic enzymes, cytokines, and chemokines released by inflammatory cells. These substances can damage the epithelial barrier and cause changes in the airway epithelium, impacting the body's ability to defend against infection. This damage can make people more susceptible to bacterial and viral infections, triggering COPD exacerbations and contributing to disease progression. Recent research has linked vitamin D deficiency to COPD exacerbations [8]. However, studies indicate that only individuals with 25(OH) D levels below 25 nmol/L can benefit from vitamin D supplements in reducing exacerbations [105, 108, 109, 126, 127]. Undoubtedly, a thorough investigation is necessary to fully understand the mechanism through which vitamin D supplementation provides its protective effect.

In another aspect, adequate local levels of 1,25(OH)2D can offer partial defense against the consequences of exposure to inhaled oxidants or those generated by recruited inflammatory cells; 1,25(OH)2D can reduce oxidative stress and helps maintain the integrity of the epithelial barrier and regulate immune responses. Moreover, vitamin D helps protect against the adverse effects of both bacterial and viral infections by promoting antiviral responses, increasing the expression of antimicrobial peptides (AMPs), and regulating inflammatory responses. Additionally, proper vitamin D intake can significantly enhance the body's ability to fight off diseases and minimize the risk of adverse outcomes. Furthermore, pairing vitamin D with anti-inflammatory or anti-fibrotic drugs has proven to be an effective treatment method. This technique explicitly targets cytokines and proteins that can decrease levels of 1,25(OH)2D and stimulate the expression of activating enzymes.

Future research should prioritize enhancing local 1,25(OH)2D levels in chronic inflammatory diseases associated with vitamin D deficiency, such as COPD. This approach can help prevent the adverse effects of increased calcium levels and immune system inhibition. Ultimately, this can lead to the creation of more efficient treatment methods.

On the other hand, it is worth considering how taking VD supplements can impact the diversity of gut bacteria and the production of short-chain fatty acids (SCFAs). SCFAs have been shown to have a protective effect on the immune system of patients with COPD, which can slow down the progression of the disease and reduce the number of flare-ups. In the future, more research is needed to determine if VD supplements can protect against chronic inflammatory conditions by changing gut or lung bacteria.

Abbreviations

VD	Vitamin D
VDR	Vitamin D receptor
VDREs	Vitamin D receptor elements
VDBPs	Vitamin D binding proteins
COPD	Chronic obstructive pulmonary disease
AMPs	Antimicrobial peptides
RCTs	Randomize control trials
SCFAs	Short chain fatty acids
UVR	Ultra violet rays
PTH	Parathyroid hormones
Th cells	T-helper cells
IL	Interleukin
TNF-α	Tumor necrosis factors alpha
RV	Residual volume
TLC	Total lung capacity
ICS	Inhaled corticosteroid
SR	Steroid resistance
IBD	Inflammatory bowel disease
CAMP	Cyclic adenosine monophosphate
ASL	Airway surface liquid
T-regs	Regulatory T cells
BMI	Body mass index
TGF-β1	Transforming growth factor-beta1
FGF-23	Fibroblast growth factor 23
CF	Cystic fibrosis

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Authors' contributions

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Availability of data and materials

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Declarations

Consent for publication

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Competing interests

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