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REVIEW

The Role and Clinical Significance of Vitamin D in Chronic Obstructive Pulmonary Disease

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Abstract: Vitamin D is well known for its role in bones, but it also has a variety of extra-skeletal effects. Vitamin D deficiency is becoming a global health problem. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the world, resulting in an enormous medical and economic burden. Accumulating evidence indicates a high prevalence of vitamin D deficiency in patients with COPD, which has emerged as a significant modulator of disease progression. This comprehensive review systematically examines the multifactorial etiology of vitamin D deficiency in COPD, encompassing insufficient sunlight exposure, malnutrition, smoking, comorbidities, and chronic inflammatory states. Clinical observational studies have demonstrated significant associations between vitamin D deficiency and increased exacerbation frequency, accelerated lung function decline, and elevated mortality risk. Mechanistically, we elucidate the pleiotropic effects of vitamin D in COPD pathogenesis, including its anti-inflammatory activity, suppression of oxidative stress, modulation of innate and adaptive immunity, inhibition of hepcidin, and reduction in pulmonary infection risk. Building on current evidence, we critically evaluate the clinical efficacy of various vitamin D supplementation strategies. This review aims to provide clinicians with an evidence-based framework for incorporating vitamin D assessment and supplementation into comprehensive COPD management while also identifying key directions for future research.

Keywords: COPD, AECOPD, vitamin D, vitamin D supplement, vitamin D deficiency

Introduction

Diet-related diseases such as rickets, beriberi, osteoporosis, and scurvy have long been a burden on human health. Vitamin D, a fat-soluble vitamin mainly found in the form of vitamin D2 and vitamin D3, was discovered in the early 20th century. It is now known that vitamin D has a substantial role in calcium and phosphorus metabolism, muscle and bone health.[1] Diabetes, autoimmune diseases, and chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD).[2–7]Cardiovascular disease,[8] cancers such as lung,[9] colorectal,[10] breast,[11] and thyroid cancer,[12] and other diseases have also been found to be associated with vitamin D expression levels. Vitamin D deficiency is thus increasingly becoming a topic of particular interest in clinical and basic research.

COPD is a common, preventable, and treatable heterogeneous disease with high disability and mortality rates. In 2019, COPD caused 3.23 million deaths according to the World Health Organization (WHO) and is the third leading cause of death and the seventh leading cause of ill health globally. Almost 90% of COPD deaths among people under 70 years of age occur in low- and middle-income countries, resulting in a huge social and economic burden.[13] COPD is characterized by persistent airflow limitation and corresponding respiratory symptoms. The pathological changes associated with COPD are primarily airway pathology and alveolar abnormalities, which result in coughing, coughing up sputum, and respiratory distress.[14] Acute exacerbation (AE) of chronic obstructive pulmonary disease (AECOPD) is occurs when the condition worsens within 14 days, and is characterized by increased dyspnea and/or a cough with sputum, which may be accompanied by shortness of breath and/or tachycardia. AECOPD usually occurs, due to an

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exacerbation of local and systemic inflammatory responses resulting from infection, pollution, or other respiratory insults. When recurrent and acute exacerbations of COPD occur, patients' lung function declines further, which increases the risk of other conditions such as hyperglycemia, atherosclerosis, hypertension, dyslipidemia, and osteoporosis.[15] This further contributes to disease progression and increases the likelihood of adverse events.[16] Factors contributing to AECOPD include infections, tobacco smoke inhalation, airflow limitation, air pollution, and emotions.[17] Despite the tremendous progress made in COPD research so far, many unanswered questions remain, including the role of vitamin D.[18] Vitamin D deficiency is also prevalent in patients with COPD. The purpose of this article is therefore to summarize what is currently known about the role of vitamin D and its deficiency in COPD. We hope this will contribute to future advances in the management and treatment of this COPD and AECOPD.

Materials and Methods

We conducted a systematic literature search across PubMed, Medline, Web of Science, and EMBASE databases using a combination of MeSH terms and free-text keywords including "COPD", "vitamin D", "physiological mechanisms", "metabolism", "deficiency", and "anti-inflammatory effects", among others. Our search strategy specifically targeted high-quality evidence such as randomized controlled trials (RCTs), prospective clinical studies, and review articles, with additional examination of reference lists from retrieved publications. Following strict systematic review methodology, we carefully selected the most scientifically rigorous and clinically relevant studies to ensure the reliability of our conclusions.

Molecular Biology and Metabolism of Vitamin D

Vitamin D is a fat-soluble, open-ring steroid that comes in a variety of forms, of which vitamin D2 (ergocalciferol) and vitamin D_3 (cholecalciferol, the most biologically active form), predominate in the human body. Both can be obtained from food and supplements. Vitamin D_3 in the human body is primarily derived from 7-dehydrocholesterol in the skin after exposure to ultraviolet light, which is transformed into vitamin D_3 precursors that are converted to vitamin D_3 by thermotropic action.[19] Of the vitamin D present in food, vitamin D_2 is primarily in plants, fungi, and yeast, while vitamin D_3 is from animals.[20] Endogenous vitamin D, by virtue of its lipophilic nature, readily traverses cellular membranes to enter capillary networks, where it rapidly associates with vitamin D-binding protein (DBP) in the circulation. This enables its systemic distribution and subsequent metabolic utilization.[21] This direct absorption pathway confers high bioavailability while remaining independent of digestive function. In contrast, dietary vitamin D absorption requires coordinated digestive processes. Following gastric emulsification with dietary lipids, vitamin D depends on bile acid-mediated formation of mixed micelles, primarily in the duodenum and proximal jejunum,[22] which facilitates its solubilization in the aqueous intestinal milieu.[23] The vitamin then crosses the enterocyte brush border membrane via nonsaturable passive diffusion. Within enterocytes, it undergoes re-esterification and incorporation into chylomicrons,[24] ultimately entering systemic circulation via lymphatic transport through the thoracic duct.[25]

Two main hydroxylation reactions occur in the liver and kidneys during vitamin D synthesis, 25 hydroxylase-catalyzed synthesis of 25-OH-D (25-hydroxycholecalciferol, also known as calcidiol), occurs in the liver. This is the primary form of stored vitamin D in the body, and its levels reflect the body's nutritional state and serum levels of vitamin D. Approximately 99% of 25-OH-D undergoes highly efficient reabsorption in the renal proximal tubule epithelial cells through the megalin-cubilin receptor system.[26] This physiological process effectively prevents urinary loss of this active metabolite. Ultimately, this metabolic pathway is tightly regulated by a sophisticated hormonal network, including parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and serum calcium-phosphorus levels.[21] 25-OH-D undergoes hydroxylation in the kidney via 1α- hydroxylation by the 1α-hydroxylase CYP27B1 to 1,25-dihydroxy vitamin D ($1,25(OH)_2D$), also known as calcitriol. Although the majority of 1α-hydroxylase activity occurs in the kidney, this enzyme is also expressed in other cells, including macrophages, monocytes, and muscle fibers. $1,25(OH)_2D$ is the primary active metabolite of vitamin D in the body; it binds to vitamin D-binding protein (DBP) for transportation to target organs and tissues, where it binds to the widely-expressed vitamin D receptor (VDR) to exert its effects. 25-OH-D and $1,25(OH)_2D$ undergo enzymatic catabolism in the kidney through CYP24A1-mediated hydroxylation to form water-soluble metabolites such as 24,25-dihydroxyvitamin D, which are subsequently excreted via biliary

and urinary pathways.[27] Beyond the classical active form 1,25(OH)2D, emerging evidence indicates that other vitamin D metabolites exhibit varying degrees of biological activity. Notably, CYP11A1-derived hydroxylated metabolites, including 20S(OH)D3 and 22(OH)D3, demonstrate non-calcemic biological effects.[28] These discoveries have opened new avenues for investigating vitamin D physiology and developing novel vitamin D analogs with selective biological activities.

DBP is a nucleophilic intranuclear protein produced primarily by the liver that mediates the biological effects of $1,25(OH)_2D$ and thus plays a critical role in the action of vitamin D.[29] Most circulating 25(OH)D and $1,25(OH)_2D$ are tightly bound to DBP, with a small amount (10–15%) bound to serum albumin. Less than 1% of circulating vitamin D metabolites exist in a free, unbound form; unbound free 25(OH)D is biologically active.[30] The high binding affinity of DBP for vitamin D and its metabolites helps to maintain adequate serum levels of vitamin D.[31]

VDR is present in various cells and tissues, including bone, immune, skin, brain, gonad, stomach, heart, and pancreatic tissues.[32] Consequently, vitamin D deficiency can impair the function of these organs, leading to the onset of multiple associated diseases, including cardiovascular conditions, malignant tumors, autoimmune disorders, neuropsychiatric illnesses, and endocrine dysfunction.[33]

Vitamin D Deficiency

Analytical methods for measuring vitamin D in the human body have yet to be standardized.[34] The techniques employed for quantifying total 25(OH)D include radioimmunoassay (RIA), high-performance liquid chromatography (HPLC), liquid chromatography-tandem mass spectrometry (LC-MS), and chemiluminescent immunoassay (CLIA). Among these, LC-MS is currently regarded as the most accurate and reliable method.[30] In addition, the international definition of vitamin D deficiency remains a subject of debate on a global scale.[35] Varying recommendations from different societies stem from the assessment of diverse clinical and public health strategies. It is currently acknowledged both in China and internationally that serum 25-OH-D levels below 20 μg/L (50 nmol/L) are indicative of vitamin D deficiency, while levels between 20–30 μg/L (50–75 nmol/L) signify vitamin D insufficiency. Levels exceeding 30 μg/L (>75 nmol/L) are classified as adequate, and those below 10 μg/L (<25 nmol/L) represent severe deficiency.[36] Patients with COPD do not always undergo vitamin D testing in clinical settings; in one hospital in Spain, only 44% of patients with severe COPD screened into a study cohort underwent testing for vitamin D levels. Furthermore, more than half of these patients tested were found to be deficient in vitamin D.[37] Approximately 40% of Europeans are reported to experience vitamin D deficiency, 13% of whom suffer from severe deficiency. Contributing factors include insufficient sunlight exposure and inadequate dietary intake of foods rich in vitamin D; risk factors that may contribute to or exacerbate vitamin D deficiency include obesity, advanced age, malabsorption syndromes, pregnancy, and darker skin pigmentation.[38] Russian researchers conducted a study in which levels of 25(OH)D were measured in 13,040 Russian adults between 2013 and 2018; 34% of the study population had 25(OH)D levels in the 10–20 μg/L range, while 5.6% had levels below 10 μg/L.[39] Furthermore, vitamin D levels were found to be associated with age, season, and geographical location. Vitamin D deficiency is also widespread in China; an analysis of a random sample of 6273 adults aged 60 years or over and found that up to 58.3% of individuals had vitamin D levels below 20 μg/L.[40] This research suggests vitamin D deficiency is a global health issue affecting individuals across all age groups.

Epidemiologic Study of Vitamin D in COPD

The role of vitamin D in the acquisition and prognosis of AECOPD have not been definitively established; however, numerous studies indicate that AECOPD is associated with vitamin D deficiency. A cross-sectional study revealed a high prevalence of vitamin D deficiency among individuals with COPD, particularly those with severe forms and during episodes of acute exacerbation.[41] A Turkish study reported vitamin D deficiency in 115 of 117 patients with COPD (98.3%),[42] while Maria Minter et al established that reduced vitamin D levels occur more frequently in patients with COPD than in healthy individuals.[43] Extensive epidemiological data suggest that vitamin D deficiency may serve as a modifiable risk factor for COPD development and progression. Notably, a US study of 1609 patients with COPD identified vitamin D deficiency in 21% of participants, with deficient individuals exhibiting higher rates of AECOPD, lower baseline FEV1 values, and more rapid lung function decline.[44] Supporting these findings, Zhu et al's analysis of

UK Biobank data demonstrated an inverse correlation between vitamin D levels and both COPD incidence and mortality risk.[45] Korean researchers further observed vitamin D deficiency in 193 of 329 patients with COPD (58.7%), with the deficient group showing significantly higher CAT scores, particularly for symptoms such as sputum production, chest tightness, exertional dyspnea, activity limitation, and fatigue.[46] Prospective cohort analyses by Gitte Færk et al revealed that individuals with severe vitamin D deficiency (<12.5 nmol/L [5 ng/mL]) had markedly increased all-cause mortality,[47] while additional studies found patients with COPD exhibiting profound deficiency (<10 ng/mL) showed significantly greater progression of CT-quantified emphysema compared to vitamin D-sufficient counterparts.[48] These collective findings underscore both the high prevalence of vitamin D deficiency in COPD populations and its association with poorer clinical outcomes, with deficiency becoming particularly pronounced during AECOPD episodes.

The decreased vitamin D levels observed in patients with COPD may result from disease-related appetite suppression and reduced sunlight exposure (including diminished cutaneous synthesis efficiency due to air pollution),[49] which directly limit vitamin D acquisition and may contribute to nutritional deficiencies.[50,51] During infectious or chronic inflammatory states (such as autoimmune disorders or persistent infections), the immune response accelerates vitamin D consumption, while inflammatory cytokines (particularly TNF-α and IL-6) downregulate 1α-hydroxylase expression, thereby inhibiting vitamin D activation and exacerbating deficiency-related pathophysiological consequences.[52] Comorbid conditions such as chronic kidney disease and diabetes further reduce active vitamin D levels through multiple pathways: impaired 25- or 1α-hydroxylation, abnormal sequestration in adipose tissue, and increased urinary excretion of vitamin D-binding protein due to proteinuria.[53,54] During acute exacerbations, the combination of increased vitamin D demand and diminished reserves creates a vicious cycle that worsens both immunosuppression and metabolic dysregulation. Smoking—a well-established COPD risk factor—[14] has been consistently associated with lower serum vitamin D levels and disrupts vitamin D homeostasis through multiple mechanisms:[55] tobacco-derived toxins not only reduce cutaneous vitamin D synthesis under UV radiation and enhance hepatic catabolism but also impair intestinal vitamin D absorption while suppressing its bioactivation through chronic inflammation induction.[51,56] Notably, a significant recovery in serum vitamin D levels can be observed shortly after smoking cessation. This phenomenon provides further validation for the mechanistic link between tobacco exposure and vitamin D metabolic dysregulation.[57] These findings not only establish direct evidence for the causal relationship between smoking and vitamin D deficiency, but also highlight the positive clinical implications of smoking cessation for improving vitamin D nutritional status.

In addition, therapeutic interventions and combinations of medications used in the management of COPD, such as glucocorticoids, may also lead to a reduction in vitamin D levels. Glucocorticoid-induced osteoporosis (GIO) is the most common type of secondary osteoporosis, with GCs potentially accelerating the degradation of vitamin D.[58] Inhaled corticosteroids (ICS) are effective agents for managing airway inflammation in patients with severe COPD, as they reduce inflammation and enhance lung and other organ function However, the use of glucocorticoids is associated with reduced serum vitamin D levels in patients diagnosed with asthma.[59] In individuals diagnosed with COPD, the utilization of ICS may also contribute to bone loss, osteoporosis, and diminished vitamin D levels.[60]

The Role of Vitamin D in COPD

Acute exacerbations of COPD are commonly associated with respiratory infections. Vitamin D has significant role in human metabolism and anti-inflammatory processes,[61] so there is research interest its potential impact on COPD. However, the underlying mechanisms have not yet been fully elucidated (See Figure 1).

Anti-Inflammatory Activity

Vitamin D protects epithelial cells from exposure to lipopolysaccharides (LPS) and thus enhances their viability.[62] When pathogens invade the respiratory tract, LPS binds to toll-like receptor-4 (TLR4) molecules on macrophages.[63] This interaction triggers regulatory pathways within the cell, leading to the phosphorylation of IκBα and P65, and the activation of NF-κB and AP-1 signaling pathways, which subsequently elicit inflammatory responses.[64] Vitamin D has been shown to inhibit these pathways and downregulate inflammatory factors.[65] In vivo studies indicate that localized 25 (OH)D at infection sites is converted into 1,25(OH)D via the enzyme CYP27B1 in immune cells such as macrophages.[66] This active form then binds to VDR expressed by airway epithelial cells. Activated VDR prevents the translocation of

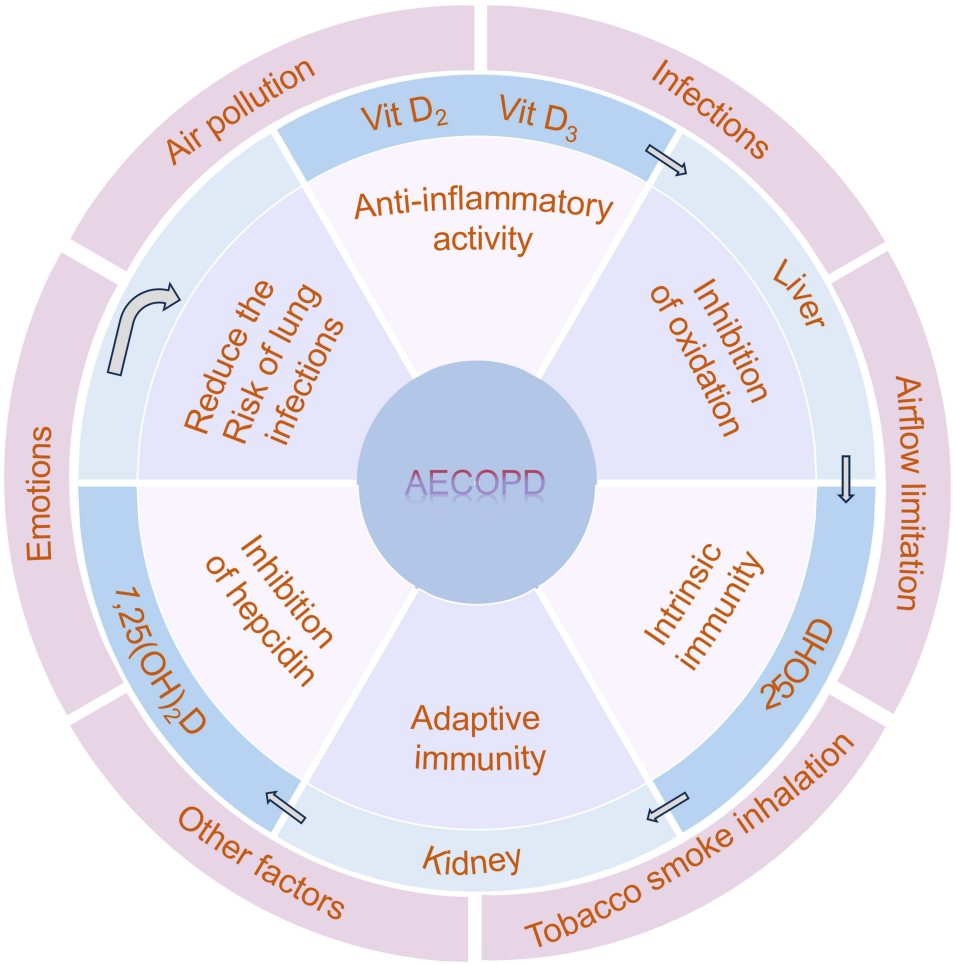

Figure 1 Diagram of the mechanism of action of vitamin D in acute exacerbation of COPD.

NF-κB and AP-1 from the cytoplasm into the nucleus. By binding to specific DNA response element sequences and activating gene transcription, this process ultimately suppresses inflammation.[67,68] Emerging evidence indicates that certain monohydroxylated vitamin D metabolites possess significant biological activities. Notably, 20S(OH)D_3 demonstrates biological effects comparable to the classical active form 1α,25(OH)$_2D_3$,[69] while 22(OH)D_3 exhibits potent anti-inflammatory and immunomodulatory properties.[28]

Inhibition of Oxidation

Activation of TLRs not only triggers an inflammatory response but also stimulates the production of antimicrobial peptides (AMPs) and reactive oxygen species (ROS), which are essential for pathogen elimination.[70] However, excessive ROS in conjunction with inadequate antioxidant defenses can lead to the oxidation of proteins, lipids, and DNA, and have detrimental effects on cells. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase produces a significant amount of ROS; vitamin D has been shown to reduce NADPH oxidase activity, thereby decreasing ROS production, while upregulating antioxidant enzymes such as superoxide dismutase, enhancing antioxidant levels. Vitamin D also mitigates excessive mitochondrial division and enhances mitochondrial adenosine triphosphate (ATP)ase activity, further reducing ROS accumulation.[71] This provides protection against oxidative stress.[72]

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Intrinsic Immunity

Antimicrobial peptides are important components of the body's intrinsic immunity. These peptides include cathelicidins and β-defensins, which contribute to the intracellular elimination of microorganisms.[73] LL-37 is the sole cathelicidin-like antimicrobial peptide identified in humans. In addition to its antimicrobial properties, LL-37 facilitates the recruitment of T cells, neutrophils, monocytes, and macrophages into infected epithelial cells, promoting apoptosis, autophagy, and ultimately the clearance of respiratory pathogens. Furthermore, vitamin D can stimulate the transcription of antimicrobial peptides and augment their expression through both autocrine and paracrine mechanisms, thereby achieving antimicrobial effects.[74] Together, these processes enhance the body's capacity to combat harmful microorganisms.[75]

Adaptive Immunity

In an adaptive immune response, monocytes, macrophages, dendritic cells, and other antigen-presenting cells activate effector cells such as T and B lymphocytes, which then perform various functions associated with the immune response. T helper (Th) cells of different types have distinct roles: Th1 cells produce cytokines such as interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ that promote inflammatory responses. In contrast, Th2 and Th10 cells inhibit inflammation. An imbalance between Th1- and Th2-induced cytokines is strongly linked to the development of infections and inflammatory diseases, including COPD.[76] Vitamin D inhibits pro-inflammatory states by interacting with antigen-presenting cells, directly and indirectly promoting the differentiation of regulatory T cells (Treg),[77] and mitigates the risk of tissue damage resulting from excessive Th1 activity.[78]

Inhibition of Hepcidin

The antimicrobial protein hepcidin (HAMP) inhibits iron transporter proteins, which are integral membrane proteins responsible for exporting intracellular iron that play a crucial role in maintaining iron ion homeostasis. Inflammatory factors can stimulate the production of hepcidin, thus reducing the availability of iron throughout the body.[79] Iron is essential for the growth and maintenance of virtually all microorganisms; thus, a key strategy in mammalian antimicrobial defenses involves depriving pathogens of this vital nutrient.[80] Activated VDR directly represses genes involved in iron modulation within monocytes and hepatocytes,[81] leading to increased expression of iron transporter proteins and decreased ferritin expression. This regulatory mechanism promotes enhanced iron export, increases overall iron availability, and ultimately inhibits bacterial growth.

Reduce the Risk of Lung Infections

The renin-angiotensin system (RAS) comprises two primary axes. Activation of the ACE/Ang-II/AT1R axis is associated with the promotion of inflammation within the respiratory system, while activation of the ACE2/Ang-(1-7)/Mas axis inhibits pro-inflammatory signaling, mitigates oxidative stress, and exerts other beneficial effects.[82] Angiotensin-converting enzyme 2 (ACE2), a crucial regulator of RAS, cleaves Angiotensin II (AngII) into the peptide Ang(1–7), which controls internal infections.[83] Viral infections are known to downregulate ACE2 levels, whereas vitamin D and its hydroxylated metabolites modulate both RAAS activity and ACE2 expression. By inhibiting viral interaction with ACE2 and promoting the ACE2-Ang-(1-7)-Mas axis, these compounds help mitigate infection severity and limit pulmonary damage during viral infections.[84,85]

Vitamin D Therapy

The prevalence of vitamin D deficiency and its associated complications is increasing, impacting the health of individuals across all demographics; vitamin D supplementation is one option for mitigating this. Different populations require varying levels of vitamin D supplementation. Individuals who have gastrointestinal disorders, infections, malignant tumors, diabetes, osteoporosis, obesity, and other conditions generally require higher levels of vitamin D compared with those in good health.[86] The question of whether to supplement with vitamin D2 versus vitamin D3 remains a topic of debate. Compared with vitamin D3, vitamin D2 has a lower affinity for vitamin D binding protein (VDBP), which may lead to a shorter half-life and lower efficacy. Additionally, the two forms of vitamin D compete for 25-hydroxylase

binding. The US Clinical Guidelines for Endocrinology thus recommend against the use of vitamin D2 when there is a specific need for supplementation.[87] Calcitriol is recognized as the most active metabolite of vitamin D. Alfacalcidol, a synthetic analog of calcitriol (1α-hydroxyvitamin D), undergoes 25-hydroxylation to form calcitriol in the liver, eliminating the need for enzymatic conversion by the renal enzyme 1α-hydroxylase.[88] Research has demonstrated that alfacalcidol effectively prevents falls and fractures in postmenopausal women with osteoporosis and in older adults.[89] Furthermore, Vitamin D has a positive impact on the treatment of COVID-19. Its administration may enhance patient outcomes, reduce reliance on additional respiratory support, and lower in-hospital mortality rates among those affected by COVID-19.[90]

Vitamin D supplementation in patients with COPD is a promising therapeutic strategy, but the role of vitamin D supplementation and the optimal dosage remain subjects of considerable debate (Table 1). A study conducted in the United Kingdom demonstrated that vitamin D supplementation significantly and safely reduced the incidence of acute exacerbations in patients with moderate to severe COPD who had baseline 25-hydroxyvitamin D levels below 25 nmol/L. However, this effect was not observed in patients with higher baseline levels. The study also indicated that vitamin D supplementation effectively decreased the frequency of acute exacerbations among individuals with moderate to severe COPD.[91]

One meta-analysis indicated that vitamin D supplementation leads to improvements in St George's Respiratory Questionnaire (SGRQ) score, which measures the extent to which an individual's health is impaired by respiratory conditions, and enhancements in lung function, improving the quality of life for patients with COPD.[92] However, another meta-analysis indicated that vitamin D supplementation did not significantly reduce acute exacerbations of COPD or improve lung function.[94] Another study also found that vitamin D supplementation at 16,800 International Units (IU) per patient per week did not significantly reduce acute exacerbation rates in patients with vitamin D-deficient COPD.[93] To prevent vitamin D deficiency within the population, it has been proposed that vitamin D deficiency be defined as 25(OH) D levels below 30 nmol/L. At elevated levels (25(OH)D $\geq$ 50 nmol/L), additional vitamin D supplementation is considered unlikely to confer further health benefits.[95] It is crucial to emphasize that vitamin D supplementation is not universally appropriate, as excessive intake may lead to adverse effects including vitamin D toxicity, hypercalcemia, and acute kidney injury.[96–98] Particular caution is warranted in high-risk populations such as patients receiving thiazide diuretics or those with granulomatous disorders (such as sarcoidosis), due to their significantly increased susceptibility to hypercalcemia (Table 2).[96,99]

Conclusion

Vitamin D deficiency is linked to numerous chronic diseases including COPD, and significantly increases the risk of infections which may result in AECOPD. The clinical outcomes and progression of COPD are heterogeneous. Accurately predicting the trajectory of COPD, including declines in lung function and the occurrence of AECOPD, remains challenging. Therefore, there is a pressing need to identify reliable biomarkers that can indicate the progression of this

Table 1 Exploring the Association of Vitamin D Between Vitamin D Supplementation and Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Trial	Conclusion
David A Jolliffe et al (2019)[91]	For patients with vitamin D less than 25 nmol/L, vitamin D supplementation reduced the rate of moderate or severe COPD exacerbations.
Yuhang Wang et al (2022)[92]	Vitamin D supplementation in patients with COPD can improve quality of life, symptoms, immune function, and SGRQ scores. For patients with asthma Vitamin D supplementation can significantly improve FEV1/FVC.
Rachida Rafiq et al (2022)[93]	Vitamin D supplementation did not help reduce the acute onset of COPD, improve quality of life and FEV1/FVC.
Ye Hua et al (2023)[94]	Vitamin D supplementation can increase serum 25 (OH) D concentration in patients, but has no significant effect on reducing COPD exacerbation and improving lung function.

Table 2 The Main Properties and Contraindications of Vitamin D

Main Properties	Specific Characteristics	COPD-Related Notes
Natural Sources	•Sunlight (cutaneous synthesis via UVB exposure).[20] •Dietary (Vitamin D2 is primarily in plants, fungi, and yeast. Vitamin D3 is from animals.[20]	COPD patients often experience reduced sun exposure due to limited mobility.
Biochemical Traits	•Precursors: Vitamin D3, Vitamin D2.[20] •Activation: Liver→25 (OH) D→Kidney→1, 25 (OH) 2D.[20]	Impaired hepatic/renal function in COPD may reduce activation efficiency.
Physiological Roles	•Calcium/phosphorus absorption → bone health.[20] •Anti-inflammatory.[67,68] •Antioxidant.[71,72] •Innate immunity.[74] •Adaptive immunity.[77,78] •Hepcidin suppression.[81] •Reduced pulmonary infection risk.[84,85]	Immunomodulation is critical for preventing COPD exacerbations.
Contraindications	•Hypercalcemia.[96] •Vitamin D toxicity.[97,98] •Sarcoidosis (granulomatous disease).[99] •Renal impairment (eGFR <30).[98] •Concurrent thiazide diuretics.[96] •High-dose calcium co-supplementation.[96]	COPD patients with sarcoidosis or thiazide diuretic use require caution.
Overdose Risks	•Chronic excess → hypercalcemia, renal injury, tissue calcification.[96,98]	COPD patients with frequent exacerbations need regular serum vitamin D monitoring.

Abbreviations: AE, Acute exacerbation; AMP, Antimicrobial peptides; COPD, Chronic obstructive pulmonary disease; DBP, D-binding protein; GIO, Glucocorticoid-induced osteoporosis; HPLC, High-performance liquid chromatography; ICS, Inhaled corticosteroids; NADPH, Nicotinamide adenine dinucleotide phosphate; RAS, Renin-angiotensin system; ROS, Reactive oxygen species; SGRQ, St George's Respiratory Questionnaire; VDBP, Vitamin D binding protein; VDR, Vitamin D receptor; WHO, World Health Organization;

disease. A better understanding of such biomarkers would not only facilitate early predictions of disease prognosis, but also enable interventions that may slow disease progression, mitigate associated tissue and organ damage, and enhance patients' quality of life. Vitamin D supplementation may be an affordable, convenient, and safe therapeutic option, particularly for individuals with multiple underlying health conditions living in economically disadvantaged areas. Clinical trials are required to determine the optimal dosage, frequency, and formulation of vitamin D supplementation, as individual requirements for vitamin D vary significantly; patients with COPD who have other comorbid conditions will likely require a personalized treatment strategy.

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Disclosure

The authors report no conflicts of interest in this work.

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