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CASE REPORT

Effect of vitamin D supplementation on lung function in chronic obstructive pulmonary disease patients: An evidence-based case report

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is characterized by progressive and persistent airflow obstruction together with an increased chronic inflammatory response, primarily caused by environmental exposure and smoking habit. Vitamin D deficiency is associated with increased rates of exacerbation and hospitalization in COPD patients. Recent studies have indicated a direct correlation between vitamin D deficiency and the severity of COPD, suggesting that acute exacerbation could be prevented with vitamin D supplementation. Some studies propose that correcting the serum vitamin D level may improve the prognosis for COPD patients experiencing respiratory tract infections.

Objective: The aim of this study was to determine the effect of vitamin D supplementation for lung function in COPD patient.

Methods: Literature search was carried out by advanced searching on Pubmed, Cochrane Library, and Scopus using a combination of MeSH Terms and Title/Abstract. Following screening for duplications, the literature obtained then screened according to predetermined eligibility criteria. The appropriate literatures were critically reviewed and the level of evidence in accordance with the Oxford Center for Evidence Based Medicine.

Results: One meta-analysis and three randomized controlled trial (RCT) met the PICO and eligibility criteria that had been set. Three studies concluded that vitamin D supplementation enhanced lung function in COPD patient. Vitamin D deficiency is common in COPD patients, so it is recommended to check vitamin D levels before vitamin D supplementation.

Conclusion: Vitamin D administration can improve lung function and prevent acute exacerbation in COPD patients.

Keywords: COPD, lung function, vitamin D, vitamin D supplementation

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Clinical scenario

A 70-year-old patient complains of worsening shortness of breath over the past week. The patient has been diagnosed COPD for the past four years and has regular treatment. The patient has often reported experiencing dyspnea following physical exertion and upon awakening in the morning over the past month. Because they experience attacks of dyspnea frequently, the patient rarely doing activity outside the home. Patient complains of wheezing and a cough in addition to shortness of breath. There is no complaint of fever. Based on physical examination, the patient's respiratory rate is 28 breaths per minute, and oxygen saturation reaches 93%. The patient's weight is 45 kg, with a height of 165 cm, resulting in a body mass index of 16.5 kg/m2. Additional wheezing sounds are heard in both lung fields. Laboratory tests show albumin level of 2.9 g/dL and a vitamin D-25 OH level of 16.7 ng/mL, categorizing it as a vitamin D deficiency.

The patient is referred to the clinical nutrition department for nutritional therapy during treatment. During the course of treatment, the patient is provided with 5000 IU vitamin D supplementation per day, with the suggestion that this could improve the patient's lung function. The patient then asks the physician about vitamin D's advantages for lung health, as he was previously aware of its benefits for bone health.

Introduction

COPD is the top ten leading global causes of death, characterized by progressive and persistent airflow obstruction primarily caused by environmental exposure to smoke and smoking habit. COPD represents a significant global public health challenge in the 21st century. In 2005, COPD was responsible for 5% of all deaths worldwide. The Global Burden of Disease 2015 reported an alarming 11% rise in COPD-related mortality from 1990 to 2015, alongside a 44% increase in disease prevalence during the same period. If this trend persists, COPD is projected to become the third most common cause of death worldwide by 2030.[1,2] Most cases of COPD (85%) are associated with smoking. Tobacco smoke exposure triggers alterations in lung function, impeding growth, diminishing peak performance, and hastening the age-related decline.[3]

About one billion people worldwide are estimated to have 25(OH)D levels of less than 75 nmol/L.[4] COPD poses a high risk for vitamin D deficiency, which is thought to be caused by malnutrition, insufficient outdoor activity, kidney dysfunction, and high catabolism associated with steroid therapy. The occurrence of insufficient vitamin D levels among individuals with COPD ranges from 31% to 77%. Compared to a control group, COPD patients exhibit lower levels of vitamin D. Additionally, insufficient vitamin D is linked to higher rates of exacerbation and hospitalization in COPD patients.[6]

Currently, vitamin D is viewed has certain systemic effects in COPD patients. Additionally, due to its impact on gene regulation, vitamin D provides protective effects against pulmonary diseases. There is considerable interest in the potential administration of vitamin D in COPD_to improve controlled symptoms and to reduce the risk of acute exacerbation. Vitamin D deficiency is common among people with COPD, in whom it associates interdependently with worse lung function and increased risk of upper respiratory infections.[7] Evidence from two randomised controlled trials shows that vitamin D supplementation reduces the risk of acute exacerbation COPD in people with vitamin D deficiency and meta-analysis of individual participant data from RCTs shows that vitamin D supplementation reduces risk of acute respiratory infection.[8] Certain research suggests that adjusting the serum vitamin D levels could enhance the outlook for individuals with COPD.[9]

Clinical questions

P: Chronic obstructive pulmonary disease
I: Vitamin D supplementation
C: Placebo or no Vitamin D supplementation
O: Acute exacerbation

Clinical question: How are the effects of vitamin D supplementation in COPD patients?

Methods

The literature search was conducted on November 20, 2023, with advanced searching on Pubmed, Cochrane Library, and Scopus, using a combination of MeSH Terms and Title/Abstract from each PICO component and using boolean operators "OR" to increase sensitivity and "AND" to increase specificity (**Table 1**). Data extraction is performed based on the eligibility criteria and relevance to the PICO framework in the clinical scenario. We excluded articles that do not meet the inclusion criteria, not conducted in humans, and articles not available in full text. Critical appraisal was conducted on the four included articles. Critical appraisal tools and determination of levels of evidence are based on the Oxford Centre for Evidence Based Medicine.

Eligibility criteria

Inclusion criteria including subjects over 18 years of age with a diagnosis of COPD, the study used randomized controlled trial (RCT) design and systematic review/meta-analysis from RCT, the intervention is the supplementation of vitamin D, while the control group was given placebo or no vitamin D supplementation, published from 2017 to 2023, and was written in English. Exclusion criteria involve studies that were not conducted on human subjects and articles that are not accessible in full text.

Critical study method

The critical review methodology involved thoroughly all selected articles by examining the *validity*, *importance*, *applicability* (VIA) using CEBM (*Centre for Evidence Based medicine*) in accordance with the type of therapeutic study.

Results

Based on the results from the database conducted with advance searching, The author found 89 literatures, 80 literatures from Pubmed, 1 literature from Cochrane Library, and 8 literatures from Scopus. As shown in **Figure 1**, there are 1 SR/MA and 3 RCTs selected to be included in this Evidence Based Case Report. Based on criteria from the Oxford Centre for Evidence Based Medicine, the level of evidence of 1 article with the SR/MA study is level 1a, while 3 articles with the RCT study is level 1b. The subjects in 4 study articles were patients with COPD who received vitamin D supplementation in the intervention group, compared to the control group given placebo or no vitamin D supplementation, to assess the outcome of acute exacerbation. The study attributes of these articles were outlined in **Table 2**. The level of evidence for these articles is depicted in **Table 3**.

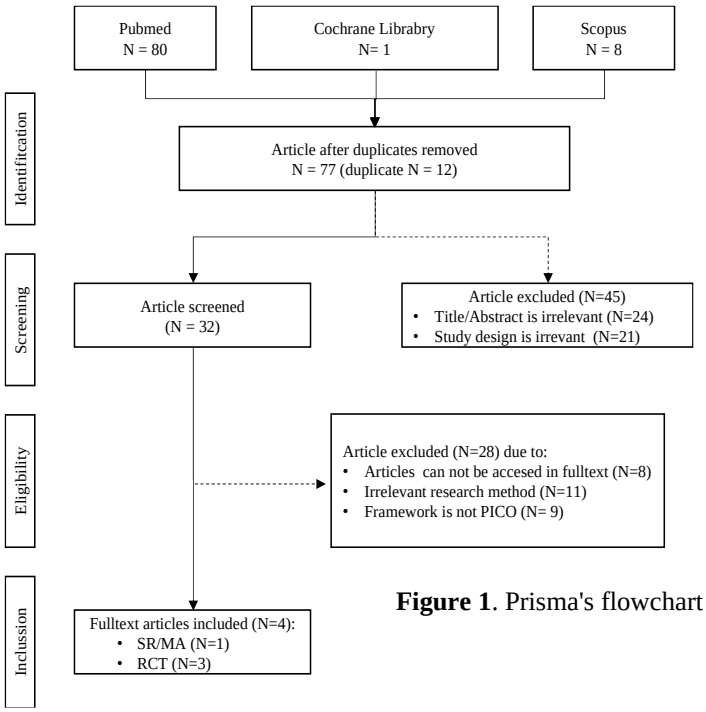

Figure 1. Prisma's flowchart

We performed an extensive review of the literature by utilizing advanced search methods on Pubmed, the Cochrane Library, and Scopus. This involved combining MeSH Terms and Title/Abstract searches. The advanced search strategy according to address the population, intervention, comparison, and outcome.

Table 1. Literature search strategy

Database	*Search Strategy*	*Hits*	*Selected Article*
Pubmed	((((((((((copd[MeSH Terms]) OR (chronic obstructive pulmonary disease[MeSH Terms])) OR (pulmonary emphysema[MeSH Terms])) OR (bronchitis, chronic[MeSH Terms])) OR (lung diseases, obstructive[MeSH Terms])) OR (copd[Title/Abstract])) OR (chronic obstructive pulmonary disease[Title/Abstract])) OR (bronchitis, chronic[Title/Abstract])) OR (pulmonary emphysema[Title/Abstract])) AND ((((((((((1 alpha, 25 dihydroxy 20 epi vitamin d3[MeSH Terms]) OR (vitamin d[MeSH Terms])) OR (cholecalciferol[MeSH Terms])) OR (cholecalciferol receptors[MeSH Terms])) OR (vitamin d receptor[MeSH Terms])) OR (vitamin d receptors[MeSH Terms])) OR (vitamin d[Title/Abstract])) OR (cholecalciferol[Title/Abstract])) OR (vitamin d receptor[Title/Abstract])) OR (vitamin d receptors[Title/Abstract]))) AND ((((((((((respiratory muscle[MeSH Terms]) OR (disease exacerbation[MeSH Terms])) OR (respiratory function test[MeSH Terms])) OR (lung function test[MeSH Terms])) OR (dyspnea[MeSH Terms])) OR (lung function[MeSH Terms])) OR (diaphragm, respiratory[Title/Abstract])) OR (respiratory muscle[Title/Abstract])) OR (disease exacerbation[Title/Abstract])) OR (lung function[Title/Abstract])) OR (respiratory[Title/Abstract]))	80	2
Cochrane Library	#1 MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] #2 MeSH descriptor: [Bronchitis, Chronic] explode all trees #3 MeSH descriptor: [Pulmonary Emphysema] explode all trees #4 MeSH descriptor: [Vitamin D] explode all trees #5 MeSH descriptor: [Cholecalciferol] 3 tree(s) exploded #6 MeSH descriptor: [Receptors, Calcitriol] this term only #7 MeSH descriptor: [Receptors, Calcitriol] explode all trees #8 MeSH descriptor: [Disease Progression] explode all trees #9MeSH descriptor: [Respiratory Function Tests] explode all trees #10#1 OR #2 OR #3 #11#4 OR #5 OR #6 OR #7 #12#8 OR #9 #13#10 AND #11 AND #12	1	1
Scopus	(((chronic AND obstructive AND pulmonary AND diseases) OR (copd) OR (pulmonary AND emphysema) OR (bronchitis AND chronic)) AND (cholecalciferol) AND (exacerbation)) AND PUBYEAR > 2017 AND PUBYEAR < 2024 AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (OA , "all")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Chronic Obstructive Lung Disease"))	8	1

Table 2. Assessment of literature characteristics

Writer	Desain Studi	Characteristics of Populasi	Intervension	Outcomes	Research Results
Xiaoyan L, et al.[10] (2020)	Meta-analysis of RCT	Total 25 articles involving 2.670 participants diagnosed as COPD according to the Guidelines for the Diagnosis and Treatment of COPD.	Patients with COPD were given vitamin D dose 125-300000 IU/week supplementation compared to placebo.	COPD assessment test, exacerbations, sputum, forced expiratory volume in 1 second, 6-minute walking distance.	vitamin D supplementation in patients with COPD could improve the lung function 6MWD and reduce acute exacerbation.
Ali AF, et al.[11] (2019)	*Randomized Controlled Trial*	30 men (93.8%) and two women (6.3%) were in the intervention group and 30 men (96.8%) and a woman (3.2%) in the placebo group.	The intervention group took 50,000 IU vitamin D_3, and those in the control group received placebo once a week for 8 weeks, then once a month for 4 months.	COPD Assessment Test (CAT) score and lung function evaluated by spirometry of patients with COPD (FEV_1, FEV_1/FVC, number of exacerbation)	Consuming 50,000 IU vitamin D_3 increased quality of life in COPD. exacerbations had not worsened after 6 months.
Rachida R, et al.[12] (2022)	*Randomized Controlled Trial*	155 COPD patient aged 40 y or older, had a vitamin D deficiency [25(OH)D concentration <50 nmol/L], and had a confirmed history of a COPD exacerbation in the last 12 month before screening.	participants were allocated in a 1:1 ratio to receive either 16,800 IU vitamin D (3 tablets of 5600 IU) or a matching placebo orally once a week for 1 year.	exacerbation rate in 1 year. Plasma C- reactive protein (CRP), and interleukin-6	The study does not show that vitamin D supplementation reduces exacerbation rate in COPD patients with vitamin D deficiency.
Farzaneh D, et al.[13] (2019)	*Randomized Controlled Trial*	70 patients (35 participants in each group) with the COPD stages of II-IV according to the GOLD report, having VDD (serum 25(OH) vita- min D level of <20ng/ml) and an age of 40 years.	The patients were randomly allocated to receive 300,000 IU of vitamin D (25-hydroxycholecalciferol) (Daropakhsh-Iran) or placebo.	the serum levels of interleukin-6, IL-8, and CRP and based on the modified Medical Research Council (mMRC) dyspnea scale.	a significant correlation was found between the change of the vitamin D levels and the degree of decrease in the level of inflammatory biomarkers, but inadequate for evaluating the clinical outcome improvements

After completing the identification and screening process, eligible articles were chosen for critical evaluation. Four articles were found to have a PICO framework aligned with the clinical scenario. Among these, three were randomized controlled trials (RCTs), while one was a meta-analysis of RCTs. These four articles identified the validity criteria based on quality and level of evidence according to the Oxford Centre for Evidence-Based Medicine (CEBM).

Table 4. Validity criteria

	PICO	Review Strategy	Study Design	Study Quality Assessment	High Quality	Results in Tables/Forest Plots	Similarity of Study Results	Quality of evidence*	Level of evidence**
Xiaoyan L, et al.[10]	+	+	+	+	-	+	+	High	1a
Ali AF, et al.[11]	+	+	+	+	+	+	+	Moderate	1b
Rachida R, et al.[12]	+	+	+	+	-	+	+	Moderate	1b
Farzaneh D, et al.[13]	+	+	+	+	+	+	+	moderate	1b

*Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly

Discussion

Vitamin D deficiency is prevalent in individuals with COPD, correlating with impaired lung function and heightened susceptibility to upper respiratory infections. There is a focus on protective factors that may mitigate the frequency and severity of COPD exacerbations. Vitamin D is particularly compelling due to its varied effects on lung health, tissue remodelling, suppression of pro-inflammatory cytokines, and beneficial modulation of both innate and adaptive immune responses.[7,14]

Based on the results of SR/MA and RCT articles show that administration of vitamin D in increased circulating concentrations of 25(OH)D. This 25(OH)D acts as a substrate for CYP27B1 expressed in the kidney and multiple extra-renal tissues, including respiratory epithelium. CYP27B1 expression in respiratory epithelium and leucocytes is induced during infection and inflammation. The active form of vitamin D, known as 1,25(OH)2D, is produced locally within the lung. It binds to the vitamin D receptor, triggering antimicrobial and antiviral responses, such as the expression of antimicrobial peptides, apoptosis, and the production of reactive oxygen and nitrogen intermediates. Moreover, this active vitamin D metabolite demonstrates anti-inflammatory properties by promoting the production of the anti-inflammatory cytokine IL-10 while inhibiting proinflammatory cytokines released by type 1 helper T cells. This combined antimicrobial, antiviral, and anti-inflammatory action holds promise for reducing the risk of acute exacerbations in COPD, which are frequently triggered by viral respiratory infections and characterized by dysregulated pulmonary inflammation.[4,8]

Several biological mechanisms may explain the contribution of vitamin D deficiency to COPD. First, vitamin D acts as a potent inhibitor in either innate or adaptive immune response via activation of VDR. Second, vitamin D can upregulate the expression of antimicrobial peptides in response to infections. Third, vitamin D deficiency has an effect on airway smooth muscle by regulating the expression of genes related to cell proliferation, glucocorticoid response, and smooth muscle contraction.[15] Vitamin D deficiency increases the

susceptibility to respiratory infections and airway colonization leading to chronic inflammation.[16]

Study from Xiaoyan L, et al.[10] and Ali AF, et al.[11] showed that vitamin D supplementation in COPD patients could reduce their acute exacerbations. Vitamin D supplementation plays a very important role in various effects on lungs, tissue remodelling, reduction of pro-inflammatory cytokines and beneficial modulation of both innate and adaptive immune systems. Study Farzaneh D, et al.[13] show vitamin D supplementation can decrease in the level of inflammatory biomarkers. Increased inflammation in COPD patients affected disease progression and exacerbation and could worsen comorbidities. Relatively, short duration of monitoring had been inadequate for evaluating the maximum effects of vitamin D on the clinical outcome improvements, including acute exacerbation. However, different results were obtained from study from Rachida R, et al.[12] studied COPD patients with ≥1 exacerbations in the preceding year and a vitamin D deficiency (15–50 nmol/L) were randomly allocated in a 1:1 ratio to receive either 16,800 International Units (IU) vitamin D3 or placebo once a week in 1 years. In this study Vitamin D supplementation did not reduce exacerbation rate in COPD patients with a vitamin D deficiency.

Vitamin D has antimicrobial antibacterial and antiviral effects through several mechanisms, one of them is the control of activity of cathelicidin which is an antimicrobial polypeptide. Cathelicidin was shown to be active against mycobacteria and against other organisms causing COPD exacerbations including antibiotic resistant strains such as Pseudomonas aeruginosa, Staphylococcus aureus, chlamydia, and other groups of viruses. This mechanism could be an explanation for the increased frequency and severity of exacerbations associated with low vitamin D in COPD.[2,16]

Many COPD patients experience vitamin D deficiency, increased rates of exacerbation and hospitalization in COPD patients are attributed to vitamin D deficiency. Recent studies have concluded that vitamin D deficiency is directly related to the severity and acute exacerbation of a COPD patients and may be prevented with vitamin D supplementation. Some studies have suggested that prognosis for COPD patients who are suffering from respiratory tract infections may improve through correction of their serum vitamin D level. Different articles might draw different conclusions due to the dose of vitamin D used, the method of administering vitamin D, and individual differences, including age, gender and race.[10] Optimal body vitamin D status is very important to maintain lung function and prevent acute exacerbations of COPD. Fulfilment of vitamin D needs can be obtained from food sources and sun exposure.[16]

Foods rich in vitamin D include fatty fish such as trout, salmon, tuna, and mackerel, with fish liver oil being the top source. Beef liver, egg yolks, and cheese offer minimal amounts of vitamin D, particularly in the form of vitamin D3 and its metabolite 25(OH)D3. Additionally, low-fat or fat-free milk and egg yolks also contain vitamin D.[17] Many individuals worldwide fulfil a portion of their vitamin D requirements through exposure to sunlight. Type B ultraviolet (UVB) radiation, ranging from about 290 to 320 nanometers in wavelength, penetrates uncovered skin and converts 7-dehydrocholesterol into provitamin D3, subsequently transforming into vitamin D3. Some experts and researchers suggest approximately 5 to 30 minutes of sun exposure, particularly between 10 a.m. and 4 p.m., either daily or twice weekly, to the face, arms, hands, and feet without sunscreen to facilitate adequate vitamin D synthesis.[18]

A recent meta-analysis and systematic review conducted in 2017 revealed a notable protective effect of vitamin D supplementation in reducing the risk of acute respiratory tract infections, particularly among individuals with insufficient vitamin D levels.[9] Based on the critical studies above, it is recommended to check vitamin D levels before vitamin D supplementation. There is considerable variation from person to person, proper dosage should be determined by measuring a patient's vitamin D blood levels before, and several months after, taking vitamin D3 additions or increasing ultraviolet-B exposure. If there is insufficiency or deficiency, vitamin D supplementation can be given until vitamin D levels are optimal and normal.[7] Vitamin D levels above 30–40 ng/mL may reduce the risk of COPD.

patients with vitamin D deficiency can be given 2000–5000 international units per day of vitamin D3 for six months n to reduce acute exacerbations.[11,19]

Conclusion

Vitamin D levels tend to be diminished in patients experiencing acute exacerbation of COPD, and this association correlates directly with lung function, the severity of the disease, and the frequency of exacerbations. The potential of vitamin D to decrease exacerbations is notable, but its efficacy is contingent upon adequate dosage and sustained intake over an extended period. There's a need for additional research to substantiate the advantages of vitamin D supplementation in COPD management.

Conflict of interest

The authors declare there is no conflict of interest regarding this article.

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