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Review Article

Vitamin D supplementation to reduce chronic obstructive pulmonary disease exacerbation: a scoping review

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ABSTRACT

Acute exacerbations are prevalent in chronic obstructive pulmonary disease (COPD) and are associated with poor clinical outcomes. Deficiency of vitamin D, a nutrient well-known for its immunomodulatory and anti-inflammatory properties, is relatively common in patients with COPD. Yet, researches on the role of vitamin D in the management of COPD exacerbations have yielded conflicting results. This systematic review aims to thoroughly investigate the effectiveness of vitamin D supplementation in reducing COPD exacerbations. The PubMed, Embase, and Cochrane databases were searched from inception to 14 March 2024. All clinical trials comparing the efficacy of vitamin D supplementation versus placebo that reported incidence of acute exacerbations as their primary or secondary endpoints were included. Eight randomized controlled trials (RCTs) involving 1,254 COPD patients were included in the analysis. Study durations ranged from 6 months to 3.3 years. The dosage regimen of vitamin D supplementation varied widely, from 1,200 IU daily to 100,000 IU monthly. Five studies reported significant reduction in COPD exacerbations ($p<0.05$), with two of them noting significant reductions only in patients with severe vitamin D deficiency. Three studies found no significant difference in exacerbation rate. Vitamin D supplementation generally reduced COPD exacerbation rate, particularly in patients with severe vitamin D deficiency. Further clinical studies are required to determine the optimal and safe dosage regimen for this special population.

Keywords: COPD, Exacerbation, Vitamin D

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a significant health and economic challenge in the Asia-Pacific region, similar to its global impact. A recent survey across nine Asia-Pacific countries found that the prevalence of COPD was 6.2%.[1] For many individuals with COPD, stable periods are interrupted by acute symptom flare-ups known as exacerbations. Around 75% of COPD patients experience at least one exacerbation annually, with frequent exacerbations defined as two or more per year.[2,3] Both reported and unreported acute exacerbations of COPD (AECOPD) have a severe and lasting effect on patients' health, leading to worsened outcomes. These exacerbations contribute to high mortality and morbidity rates, decreased quality of life, and progressive loss of lung function. Additionally, exacerbations result in considerable healthcare utilization and associated costs.[4,5]

Vitamin D deficiency is a common concern among adults and could be a contributing factor to respiratory diseases. It is linked to impaired lung function and emphysema.[6] Research through epidemiological and observational studies indicates a connection between blood vitamin D levels and clinical outcomes in patients with COPD). Other studies have also highlighted a relationship between low plasma vitamin D levels and COPD exacerbations.[7-9] Vitamin D has been proposed as a potential treatment for COPD due to its immunomodulatory properties.[10] Its

interest is particularly notable for its wide-ranging effects on lung health, tissue remodelling, reduction of inflammatory cytokines, and positive regulation of both the innate and adaptive immune responses.[11]

Our study seeks to thoroughly examine the potential benefits of vitamin D supplementation in minimizing COPD exacerbations.

METHODS

Scoping reviews aim to provide an overview of existing research on a specific topic or issue. Before conducting the literature search and data collection, the review methodology was developed following the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR). This approach consisted of five key steps: defining the research question (in this case, exploring scientific evidence on the use of inspiratory muscle training in lung cancer patients), searching for relevant studies, acquiring the studies, retrieving and organizing the data, and finally presenting the results.[12,13]

Search strategy

The research question and search strategy were formulated using the PCC framework (P: population, C: concept, C: context). Two reviewers independently conducted searches of the PubMed, Embase, and Cochrane databases from their inception until 25 November 2024. The search terms included "chronic obstructive pulmonary disease," "vitamin D," and "exacerbations," along with related keywords. To maintain consistency and minimize bias, these terms were used both individually and in combination, in line with the specific requirements of each database. The searches applied "AND" and "OR" operators and were not restricted by a specific time frame. Additionally, reference lists from the included studies were manually reviewed to identify additional relevant research.

Eligibility criteria

Inclusion and exclusion criteria were defined before initiating the searches. All clinical studies examining the effectiveness of vitamin D supplementation in reducing COPD exacerbations were included. Studies investigating vitamin D in combination with other micronutrients were excluded, as were articles not published in English. The titles and abstracts of the identified papers were organized, and duplicates were removed. Two reviewers independently assessed the titles and abstracts of the studies to select those relevant to the research.

Data extraction

To complete the review sample, both reviewers systematically evaluated the articles based on their eligibility criteria. We extracted and presented key details such as authorship, publication year, study methods (including design, participants, and interventions), main findings, and conclusions. The data were then analyzed descriptively, with an emphasis on the key themes, to provide a comprehensive summary of the literature.

RESULTS

After conducting searches across various databases, 198 research papers were found. Of these, 87 duplicate articles were removed, leaving 111 unique papers. Both reviewers independently assessed the titles and abstracts of these 111 articles, leading to the exclusion of 98 publications that did not meet the inclusion criteria. The remaining 13 articles were pursued for retrieval, but one could not be accessed. The full texts of the remaining 12 articles were then reviewed to determine their relevance to the study's objectives. Following this review, four articles were excluded because they did not specifically address the use of vitamin D in COPD exacerbation. Ultimately, the scoping review included eight studies (Figure 1).

Table 1 illustrates the studies' major overview, which includes authorship, publication year, study design, participants, study intervention and duration, along with study outcome.

All eight articles included in the analysis were randomized controlled trials, involving a total of 1,254 COPD patients. The study by Khan et al reported a significant reduction in COPD exacerbations with a daily supplementation of 2,000 IU of vitamin D3 for six months.[17] This finding was consistent with earlier studies by Martineau et al and Zendedel et al, which also observed significant reductions in COPD exacerbations with vitamin D3 supplementation — 120,000 IU every two months and 100,000 IU monthly, respectively.[15,16]

A recent study by Camargo et al found no overall effect on the exacerbation rate with boluses of 200,000 IU of vitamin D3 followed by 100,000 IU monthly.[18] However, a significant reduction in COPD exacerbations was observed in individuals with severe vitamin D deficiency, defined as serum 25-(OH) D levels below 25 ng/ml. This finding aligns with a previous study by Lehouck et al, which also reported no overall impact on exacerbation rates but noted significant reductions in COPD exacerbations among participants with vitamin D levels below 10 ng/ml.[14]

Rafiq et al conducted two separate randomized controlled trials with different vitamin D3 regimens.[10,19] Their first study in 2017 used 1,200 IU of vitamin D3 daily as their intervention, while later study in 2022 used 16,900 IU of vitamin D3 weekly. Both studies found no significant difference on COPD exacerbation rate. Similarly, in a supplementation regimen by Foumani et al, where participants received 50,000 IU of vitamin D3 weekly for 8 weeks, followed by the same dose monthly for 4 months, no reduction in COPD exacerbations was observed.[20]

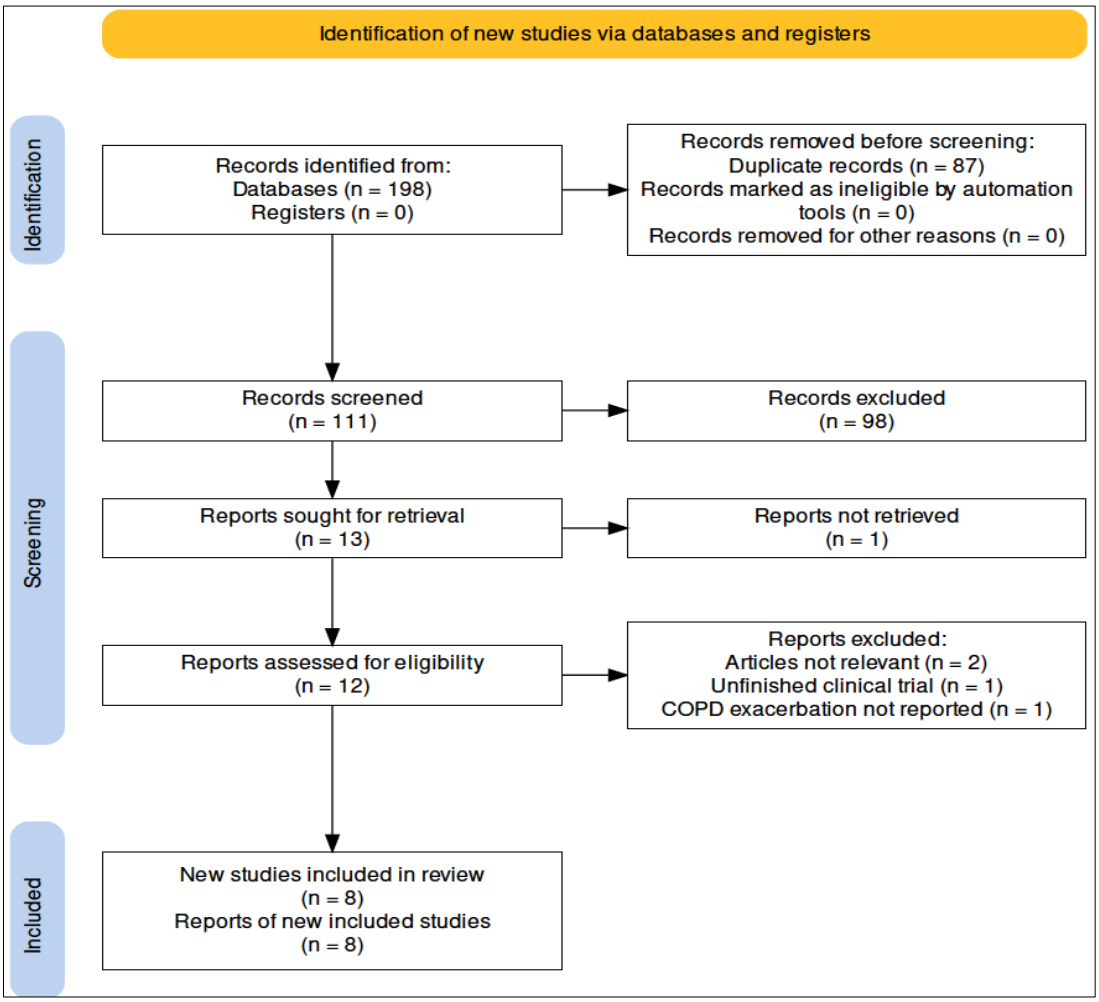

Figure 1: The PRISMA flowchart illustrating the process of resource screening and selection.

Table 1: Summary of the studies included in the scoping review.

No.	Author, year	Study design	Number of study participants (total)	Study intervention	Study duration	Outcome
1	Lehouck et al, 2012[14]	RCT	91 in vitamin D group, 91 in control group (182)	100,000 IU of vitamin D3 every month versus placebo	12 months	No overall impact on exacerbation rate. Significant reductions of COPD exacerbations among those with severe vitamin D deficiency (serum 25-[OH]D levels <10 ng/ml) (p=0.042)
2	Martineau et al, 2015[15]	RCT	122 in vitamin D group, 118 in control group (240)	120,000 IU of vitamin D3 every 2 months	12 months	Significant reductions in COPD exacerbations (p=0.021)
3	Zendedel et al, 2015[16]	RCT	44 in vitamin D group, 44 in control group (88)	100,000 IU of vitamin D3 monthly versus placebo	6 months	Significant reductions of COPD exacerbations (p<0.001)
4	Khan et al, 2017[17]	RCT	60 in vitamin D group, 60 in control group (120)	2,000 IU of vitamin D3 daily versus placebo	6 months	Significant reductions of COPD exacerbations (p=0.042)

Continued.

No.	Author, year	Study design	Number of study participants (total)	Study intervention	Study duration	Outcome
5	Camargo et al, 2021[18]	RCT	200 in vitamin D group, 156 in control group (356)	Initial bolus of 200,000 IU of vitamin D3, followed by 100,000 IU of vitamin D3 monthly versus placebo	3.3 years	No overall impact on exacerbation rate. Significant reductions of COPD exacerbations among those with severe vitamin D deficiency (serum 25-[OH]D levels <25 ng/ml) (p=0.001)
6	Rafiq et al, 2017[19]	RCT	24 in vitamin D group, 26 in control group (50)	1,200 IU of vitamin D3 daily versus placebo	6 months	No significant difference on exacerbation rate
7	Foumani et al, 2019[20]	RCT	32 in vitamin D group, 31 group in control group (63)	50,000 IU of vitamin D3 weekly for 8 weeks, followed by the same dose monthly for 4 months versus placebo	6 months	No significant difference on exacerbation rate
8	Rafiq et al, 2022[10]	RCT	74 in vitamin D group, 81 in placebo group (155)	16,800 IU of vitamin D3 weekly versus placebo	12 months	No significant difference on exacerbation rate

DISCUSSION

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.[21] COPD is considered "stable" when symptoms are effectively managed and lung function decline is decelerated. In contrast, managing "unstable" COPD, which involves frequent or severe exacerbations and a rapid deterioration in pulmonary function, can be more difficult. COPD exacerbations are a significant factor in the economic impact of the disease and, depending on their severity, may necessitate visits to the emergency department (ED) or hospital admissions.[22,23]

Vitamin D, a fat-soluble steroid hormone with biological roles and receptors in various organs, has significant effects on the human body. It is primarily produced in the skin through the conversion of 7-dehydrocholesterol to pre-vitamin D3 upon exposure to ultraviolet light. The best dietary sources of vitamin D are fatty fish and fish liver oils, while beef liver, cheese, and egg yolks contain smaller amounts. In these foods, vitamin D is predominantly in the form of vitamin D3.[24,25] Known for its role in calcium and bone metabolism, recent studies have revealed that vitamin D also plays a broader range of physiological roles.[26] This is linked to the presence of vitamin D receptors (VDR) in various cells, affecting muscle function and the immune system. These functions may have clinical relevance for patients with COPD.[27,28]

Patients with COPD are marked by an abnormal inflammatory response in the airways, with viral and bacterial infections playing a significant role in triggering exacerbations and advancing the disease. Given its potential effects on the immune system, vitamin D presents an appealing therapeutic approach for COPD. Several studies in the general population have also found a positive correlation between serum 25(OH)D levels and lung function.[29,30] Vitamin D deficiency is prevalent in 40–80% of COPD patients and is associated with the severity of the disease.[31]

Vitamin D deficiency is common among the elderly due to factors such as reduced function of the atrophic skin, limited outdoor activity, insufficient dietary intake, and decreased gut absorption, as well as impaired hydroxylation in the liver and kidneys. Since most COPD patients are elderly, the prevalence of vitamin D deficiency in those with COPD is notably high, particularly in this age group. Additionally, many chronic conditions, such as cardiovascular diseases, which often coexist with COPD, are also related to vitamin D deficiency. This suggests that vitamin D deficiency and COPD may mutually exacerbate each other, potentially facilitated by these co-occurring chronic diseases.[31,32]

Patients with severe COPD experience significantly impaired lung function, poor nutritional status, comorbid cardiovascular diseases, rib fractures, and psychological distress. They are more likely to stay indoors, have a longer history of smoking, suffer from anorexia, and use oral glucocorticoids, which further lower vitamin D levels. Vitamin D deficiency worsens severe COPD by intensifying inflammation, promoting structural changes in the lungs, reducing lung function, and increasing the risk of microbial infections.[31,33,34]

Vitamin D is believed to offer therapeutic benefits for COPD patients due to its immunomodulatory effects. It helps regulate the adaptive immune system by promoting the differentiation of immune cells into a tolerogenic phenotype and reducing the production of pro-inflammatory mediators. Additionally, vitamin D enhances phagocytosis and antimicrobial activity in innate immune cells.[10,35] Improvements in moderate or severe exacerbations may be connected to their effect in suppressing pro-inflammatory cytokines and chemokines, such as interleukin 6 and CCL5, which are involved in exacerbation development.[15] Furthermore, inadequate vitamin D levels (serum 25-hydroxyvitamin D concentration <30 ng/ml) are associated with increased vulnerability to upper respiratory infections in COPD patients. Vitamin D metabolites exhibit antimicrobial and anti-inflammatory effects in vitro, suggesting that supplementation could play a role in preventing exacerbations and upper respiratory infections in these patients.[36,37]

In patients with COPD, reduced skeletal muscle strength is frequently observed and is linked to the severity of the disease and increased mortality. Beyond its impact on the immune system, vitamin D also influences muscle function. Meta-analyses have shown a modest, yet significant, effect of vitamin D supplementation on improving skeletal muscle strength in individuals with vitamin D deficiency and the elderly.[38,39] These findings may help explain the potential benefits of vitamin D in COPD patients, particularly in preventing exacerbations.

In our scoping review, we observed that two studies found a significant reduction in exacerbation rates only in patients with severe vitamin D deficiency.[14,18] This phenomenon may reflect the heterogeneity of factors that contribute to exacerbations, a concept widely acknowledged in the field. Jollfile et al suggest that in vitamin D-deficient patients, exacerbations may primarily be driven by the deficiency itself, meaning that vitamin D supplementation helps reduce the risk of exacerbations in this group.[40] In contrast, for individuals with higher baseline vitamin D levels, other factors such as increased viral susceptibility or exposure to unidentified environmental triggers may play a more prominent role in driving exacerbation risk.

The present study has several significant strengths, including its study design (scoping review of randomized controlled trials) and good protocol adherence. However, this study includes findings from a relatively small number of trials insufficient for the purposes of generating a funnel plot to properly test for publication bias. Our findings should be explored with prudence.

CONCLUSION

In summary, we discovered that vitamin D generally reduced COPD exacerbations, particularly in patients with severe vitamin D insufficiency. Further research is needed to determine the best and safe dosing regimen for the reported benefit. To enhance the scientific value of further research, we recommend that researchers thoroughly evaluate their study population, vitamin D dose protocol, and other criteria when developing and accessing existing findings.

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