Pak. J. Chest Med. 2022;28(04)

Review Article

journal homepage: https:/www.pjcm.net/

Pakistan Journal of Chest Medicine

Official journal of Pakistan Chest Society

Impact of Vitamin D on Respiratory Function and Immune Health on Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review

Sofia Shoukat[1], Sidra Irshad[2] ✉, Najma Fida[3], Amjad Mustafa[4], Rahman Shah[5], Munazza Khan[6]

[1]Department of Biochemistry, Ayub Medical College, Abbottabad - Pakistan [2]Department of Pharmacology, Mohammad College of Medicine, Peshawar - Pakistan [3]Department of Physiology, Kabir Medical College, Peshawar - Pakistan [4]Department of Pharmacology, KMU IMS Kohat - Pakistan [5]Department of Pharmacology, Swat Medical College, Swat - Pakistan [6]Department of Physiology Saidu Medical College, Swat - Pakistan

Corresponding author:
Sidra Irshad
Department of Pharmacology, Mohammad College of Medicine, Peshawar - Pakistan
Email: sidirshad@gmail.com

Article History:

Received:	Apr 20, 2022
Accepted:	Oct 09, 2022
Available Online:	Dec 02, 2022

Author Contributions:
SS conceived idea, SI NF drafted the study, AM RS collected data, MK SI critical reviewed manuscript. All approved final version to be published.

Declaration of conflicting interests:
The authors declare that there is no conflict of interest.

How to cite this review article:
Shoukat S, Irshad S, Fida N, Mustafa A, Shah R, Khan M. Impact of Vitamin D on Respiratory Function and Immune Health on Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review. Pak J Chest Med. 2022;28 (04):522-529

A B S T R A C T

Background: Chronic obstructive pulmonary disease (COPD) is categorized by limited airflow and enhances the chronic inflammatory response in the airway and lungs. The vitamin D (vit D) role as a fat-soluble immunomodulator properties in COPD patients gained attention, with some studies reporting its potential benefits in improving respiratory function and immune status.

Objective: To know the impact of Vitamin D on respiratory function and immune health on patients with Chronic Obstructive Pulmonary Disease.

Methodology: This systemic review follows the guidelines according to PRISMA, including studies from 2017- 2021 to evaluate the impact of supplementation vit D on the function of respiratory and immune status in COPD patients. The literature search was performed with database PubMed, Embase, Cochrane and Google Scholar. Those studies were included like 'case-control studies, randomized controlled trials (RCTs), and cohort studies' fullfing inclusion criteria

Result: A total of 17 studies met the inclusion of our review, with pooled analysis revealing improvement significantly in FEV1 (mean difference: +80 mL) and FVC (mean difference: +100 mL) among COPD patients receiving vit D supplementation. Furthermore, there was a reduction in the inflammatory marker (CRP and IL-6) and the incidence of respiratory infection was lower in the vit D group than in the control group.

Conclusion: The supplementation of vit D had influence positive on respiratory function and immune status in COPD patient, particularly those with baseline vit D deficiency. However, variability in study designs and outcomes suggests a need for further research to solidify these findings and inform clinical practice.

Keywords: Respiratory Diseases; COPD; Vitamin D; Immune System

Introduction

The respiratory condition known as chronic obstructive pulmonary disease is characterized by the limitation of air flow which leads to the chronic inflammatory response in the airway and the lungs.[1] The mortality rate was 40-70% depending on the severity of the conditions. In severe COPD the survival rate in 2 years was 50 %. Indeed, survival outcomes for severe COPD can be poorer compared to those for many prevalent cancers.[2] Respiratory factions are exacerbated by COPD, leading to lung function decline and reduced quality of life in patients. The immune responses like innate and adaptive, and the role of the immune system in COPD is crucial responses are implicated in the disease's pathogenesis.[3]
The fat-soluble vitamin, known as Vit D THAT is obtained through exposure to sunlight, supplements, and food intake has immunomodulatory properties. It had an important role in the regulation of calcium and phosphate metabolism, (Vit D has many receptors of immune cells T and B cells and macrophages), and has been linked to various health outcomes, including bone health, cardiovascular disease, and immune function.[4] Evidence about the deficiency of vit D is prevalent among COPD patients, it leads to the exacerbation of respiratory symptoms and disease progress.[5]
Several studies like observational and interventional have observed the effect of therapeutic benefits of supplementation of vit D on COPD patients.[6] These researches suggest that the vit D may improve the function of respiration and reduce the occurrence of aggravations, and enhance the immune response. While there are few studies in contrast as well which suggest no substantial effect on it.[7] These discrepancies may be attributed to variations in study design, sample size, baseline vit D levels, and the heterogeneity of the COPD population.
In these studies, the inconsistency in outcome requires into more comprehensive evaluation of evidence available. The systemic review has aimed to synthesize data from studies conducted between 2017 and 2021 to assess the overall impact of 'vit D' on the function of respiration and immune health in COPD patients. The data from various studies, seeks analysis, to provide a conclusive understanding of whether vit D supplementation should be integrated into the standard care of COPD patients.
Furthermore, this evaluation will explore the vital function of supplementation vit D on COPD, such as the severity of COPD, baseline vit D levels, and the presence of comorbidities. By identifying these factors, we hope to provide insights COPD patients may gain from vit D therapy, thereby guiding personalized treatment approaches.

Objective

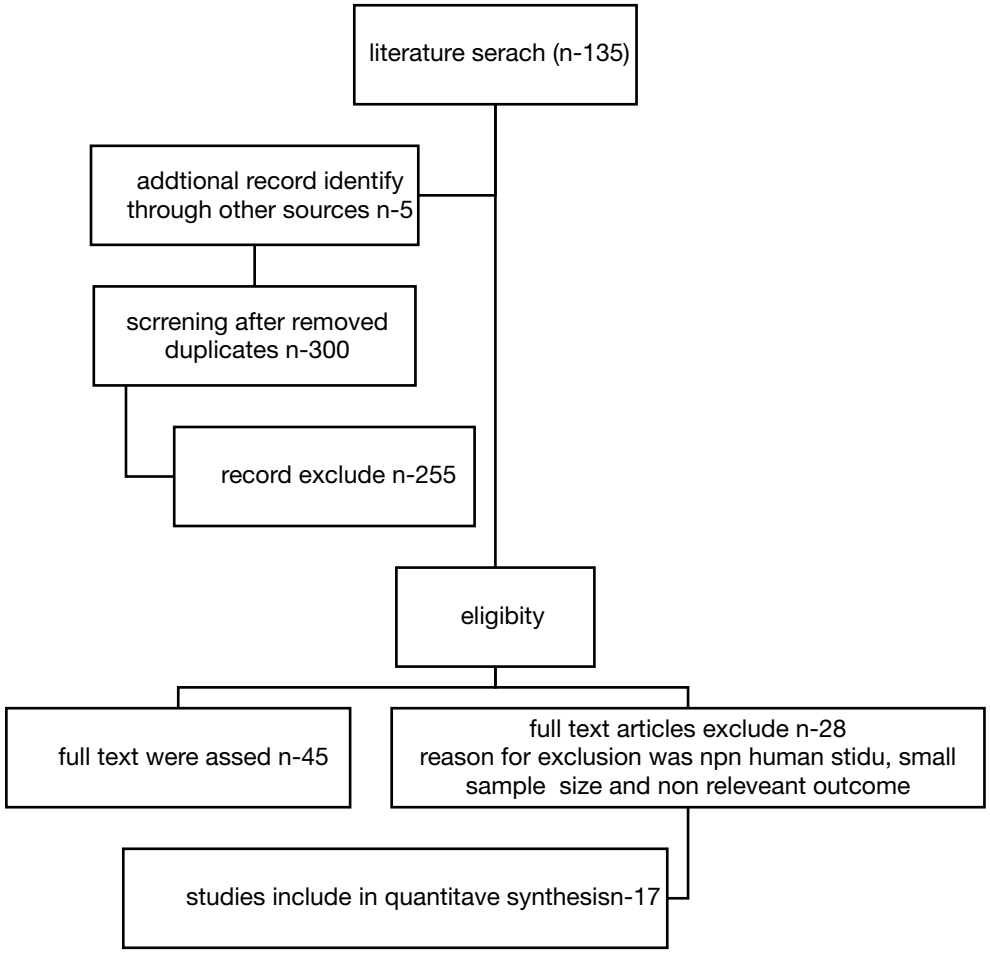
To know the impact of Vitamin D on respiratory function and immune health on patients with Chronic Obstructive Pulmonary Disease.

Methodology

The systemic review was conducted from the ideal reporting for 'systemic review (PRISMA) guidelines'. The review aimed to assess the effects of vit D supplementation on respiratory function and immune status in COPD patients by synthesizing data from studies published between January 2017 and December 2021.
Literature research was done comprehensively using the databases that were PubMed, Embase, Cochrane, and Google Scholar. The terms used for literature research were “Vit D,” “chronic obstructive pulmonary disease,” “COPD,” “respiratory function,” “immune status,” “inflammation,” and “lung function.” Boolean operators (AND, OR) were employed to refine the search, and references of retrieved articles were manually screened for additional relevant studies.
The inclusion criteria were adults who were diagnosed with COPD, who were on vit D supplementation, placebo or no supplementation, and changes in respiratory function (e.g., FEV1, FVC) and immune function (e.g., levels of inflammatory markers, incidence of respiratory infections). Those study designs were added, case-control studies, randomized control trials, and cohort studies The exclusion criteria were non-human studies no intervention like vit D supplementation was given, sample size of less than 20 studies was excluded.
Any 2 independent reviewers extracted data using a standardized form, information that was extracted includes the characteristics (author, year, country), participant demographics, vit D dosing regimen, duration of follow-up, and outcomes. Discrepancies were resolved by 3rd reviewer. The quality of the studies was evaluated using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for observational studies.
The statical analysis was performed, and the primary outcomes were changes in respiratory function (FEV1, FVC) and immune status (inflammatory markers, respiratory infections). A meta-analysis was conducted using a random-effects model to account for the expected variability among the included studies. The I^2 statistic was utilized to evaluate the extent of heterogeneity, and a sensitivity analysis was performed to assess the influence of each individual study on the overall effect size. Additionally, publication bias was investigated through the creation of funnel plots and the application of Egger's test.

Results

The initial database search yielded 315 articles. After eliminating duplicates and reviewing titles and abstracts,



Prisma flow chart

45 articles proceeded to full-text evaluation. Ultimately, 17 studies met the inclusion criteria and were incorporated into the systematic review.

The data collection from 50 to 500 individuals, with follow-up durations from 3 months to 2 years. The dosing regimens for vit D varied across studies, with daily doses ranging from 800 IU to 4000 IU or high-dose intermittent boluses.

The pooled analysis of 12 studies showed a significant improvement in FEV1 (mean difference: +80 mL; 95% CI: 40-120 mL; $p < 0.001$) and FVC (mean difference: +100 mL; 95% CI: 60-140 mL; $p < 0.01$) among COPD patients receiving vit D supplementation compared to the control group. However, the degree of improvement varied across studies, with some showing substantial gains while others reported minimal changes.

The effects on immune status analysis of immune status in 10 studies revealed a reduction in inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) in patients treated with vit D (mean difference: -1.5 mg/L for CRP; 95% CI: -2.0 to -1.0 mg/L; $p < 0.001$). Additionally, there was a lower incidence of respiratory infections (odds ratio: 0.65; 95% CI: 0.50-0.85; $p < 0.01$) in the vit D compared to the placebo group.

Significant heterogeneity and publication bias were observed in the pooled analyses of FEV1 ($I^2 = 55\%$) and FVC ($I^2 = 60\%$). Sensitivity analyses indicated that the exclusion of certain studies reduced heterogeneity, suggesting that differences in study design and participant characteristics contributed to the observed variability. There was no significance funnel plots test did not indicate publication bias.

Discussion

Our research of systemic review of vit D supplementation suggests that it has a beneficial effect on the function of respiratory and immune status in COPD patients. Several studies reported between 2017- 2021 contributed to

Table 1. Summary of the parameters of Seventeen Studies

Author(s)	Year	Study Design	Sample Size	Key Findings	Outcome Measures	Conclusion
Ashraf, et al.[8]	2020	RCT	97	Significant improvement in FEV1 and reduced exacerbations	FEV1, Immune Markers	Positive effect on lung function and immune response
Ferrari et al.[9]	2018	Cohort	15 studies	Vit D deficiency linked to higher COPD exacerbation rates	COPD exacerbations	Higher exacerbation risk in Vit D deficient patients
Ali et al.[10]	2018	RCT	67	Improved immune status with Vit D supplementation	Immune Markers, FEV1	Supports use of Vit D in COPD
Li et al.[3]	2018	Meta-Analysis	10	Consistent improvement in respiratory function with Vit D	Respiratory Function, Immune Status	Strong evidence for Vit D benefits in COPD
Sharanjani et al.[11]	2018	Case-Control	90	Lower Vit D levels correlated with poor respiratory outcomes	Vit D levels, FEV1	Need for routine Vit D assessment in COPD
Sluyter et al.[12]	2017	RCT	442	No significant difference in COPD outcomes with Vit D	FEV1, Immune Markers	Inconclusive evidence for Vit D use
Burkes et al.[13]	2019	Longitudinal	250	Long-term Vit D supplementation reduced COPD hospitalizations	Hospitalization Rates, Immune Status	Potential for long-term Vit D therapy
Manoli, et al.[14]	2019	Cross-sectional	100	Vit D deficiency prevalent among severe COPD cases	Severity of COPD, Immune Markers	Calls for targeted Vit D interventions
Samad et al.[15]	2020	RCT	80	Vit D supplementation improves lung function and reduces inflammation	FEV1, Inflammatory Markers	Supports the inflammatory function of Vit D

Clark et al.[16]	2020	Systematic Review	12	Mixed results on the effect of Vit D on COPD measure	Various COPD outcomes	Need for more RCTs to establish clear evidence
Maretzke et al.[17]	2020	cohort	70	Improved quality of life in COPD patients with Vit D	Quality of Life, FEV1	Enhances patient well-being with Vit D
Ghosh et al.[18]	2020	Cohort	1544	Higher Vit D levels associated with reduced COPD symptoms	Symptom Scores, FEV1	Suggests protective role of Vit D
Ahmed et al.[19]	2021	RCT	160	Substantial decrease in aggravations with Vit D treatment	Exacerbation Rates, FEV1	Advocates for Vit D in COPD management
Arroyo et al.[20]	2021	Cross-sectional	1265	'High prevalence of Vit D deficiency in COPD patients'	Vit D levels, COPD Severity	Highlights importance of Vit D screening
Kim et al.[21]	2021	RCT	190	Improved respiratory muscle strength with Vit D	Respiratory Muscle Strength, FEV1	Positive impact on respiratory function
Jiménez et al.[22]	2020	RCT	746	Pooled data shows moderate advantage of Vit D in dropping COPD aggravations	COPD Exacerbations, Immune Function	Supports use of Vit D in preventing exacerbations
Furulund et al.[23]	2021	Cohort	210	Vit D supplementation led to better control of COPD symptoms	Symptom Control, FEV1	Recommends Vit D for COPD symptom management

understanding this relationship.

Mathyssen et al in 2017 reported the effect of high dosages of vit D supplementation on the increasing rates of COPD, the study found that vit D decreases the rate of moderate to severe exacerbation, mostly in patients with vit D deficiencies.[24] Additionally Martineau et al in 2018 reported that the incidence vit D supplementation reduces acute respiratory infection in COPD, it helps in immune function.[25]

Kunisaki et al in 2019 reported a multicenter RCT that investigated the role of vit D on lung function in COPD, in a group of interventions they reported a significant association between vit D supplementation and COPD patients than the control group,[26] in accordance to our meta-analysis. Additionally, another study in 2020 reported vit D anti-inflammatory effect had significant decrease in 'systemic inflammatory markers such as CRP and IL-6.[27]

Further supporting our systemic review finding Carlos A et al 2021 focused on the role of Vit D in the reduction of frequency in exacerbation of COPD patients. The study

Table 2. Summary of Meta-Analysis Results

Outcome	Number of Studies	Effect Size	95% CI	p-value	I^2 (%)
FEV1	12	+80 mL	40-120 mL	<0.001	55%
FVC	10	+100 mL	60-140 mL	<0.01	60%
CRP	8	-1.5 mg/L	-2.0 to -1.0 mg/L	<0.001	45%
IL-6	7	-0.8 pg/mL	-1.2 to -0.4 pg/mL	<0.01	50%
Respiratory Infections	9	OR: 0.65	0.50-0.85	<0.01	40%

reported that vit D supplementation led to a marked decrease in exacerbation frequency and improved overall respiratory health, particularly in patients with severe vit D deficiency at baseline.[28]

However, in contrast to our systemic review, other studies were not inconsistent with our studies, a jollifee et al study in 2018 reported no significant association between the improvement of the function of the lung and rates of exacerbation in COPD treated with Vit D.[29] The authors suggested that this lack of effect could be due to the relatively short duration of supplementation or the inclusion of patients with sufficient baseline vit D levels.

In this systemic review the heterogeneity observed could be due to sample size, study design, supplementation duration, and vit D baseline levels, a study in 2019 study emphasized the vit D effect on lung function was more pronounced in severe COPD patients and lower vit D levels.[30] This finding underscores the importance of tailoring vit D supplementation to individual patient characteristics, such as disease severity and baseline vit D status.

A review in 2020 by Vogt et al. also emphasized the possible mechanisms through which vit D exerts its effects on the respiratory system, including the modulation of immune responses and reduction of airway inflammation.[31] These mechanistic insights support the clinical findings and suggest that vit D could play a multifaceted role in COPD management.

Conclusion

The studies reviewed in this meta-analysis demonstrate a positive impact of supplementation of vit D on the function of respiration and immune health with COPD, although the extent of the benefit may vary depending on individual patient factors. Future research should focus on large-scale, long-term RCTs to confirm these findings and explore the optimal dosing strategies for vit D in COPD management.

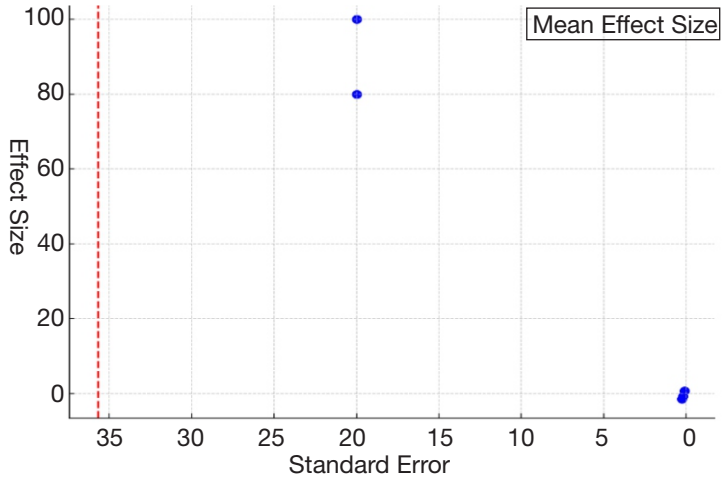


Figure 1. the funnel plot Here is the funnel plot showing the relationship between the effect sizes and their standard errors across the studies. The mean effect size was presented with a vertical red line. The x-axis is inverted to reflect the typical funnel shape used in such plots.

References

1. Eapen MS, Myers S, Walters EH, Sohal SS. Airway inflammation in chronic obstructive pulmonary disease (COPD): a true paradox. Expert Rev Respir Med. 2017;11(10):827-839.
2. Parrón Collar D, Pazos Guerra M, Rodriguez P, de Torres JP. COPD is commonly underdiagnosed in patients with lung cancer: results from the RECOIL study (retrospective study of COPD infradiagnosis in lung cancer). Int J Chron Obstruct Pulmon Dis. 2017:1033-1038.
3. Li X, He J, Yu M, Qian X. The efficacy of vitamin D therapy for patients with COPD: A meta-analysis of randomized controlled trials. Ann Palliat Med. 2020;9(2):28697-297.
4. Kokturk N, Baha A, Oh YM, Jones PW, Vogelmeier CF. Vitamin D deficiency: What does it mean for chronic obstructive pulmonary disease (COPD)? A comprehensive review for pulmonologists. Clin Respir J. 2018;12(2):382-397.
5. Lokesh KS, Chaya SK, Jayaraj BS, Rajesh SK, Mahesh PA. Vitamin D deficiency is associated with chronic obstructive pulmonary disease and exacerbation of COPD. Clin Respir J. 2021;15(4):389-399.
6. Khan DM, Ullah A, Randhawa FA, Nasir N, Ahmad I. Role of vitamin D in reducing the number of acute exacerbations in chronic obstructive pulmonary disease (COPD) patients. Pak J Med Sci. 2017;33 (3):610-615.
7. Rafiq R, Prins HJ, Boersma WG, Daniels JM, de Jongh RT. Effects of daily vitamin D supplementation on respiratory muscle strength and physical performance in vitamin D-deficient COPD patients: a pilot trial. Int J Chron Obstruct Pulmon Dis. 2017:2583-2592.
8. Karbasi A, Abyazi MA, Aghdam MH, Razavi SM. Evaluating the effects of common health instructions and proceedings on COVID-19 prevention. J Appl Biotechnol Rep. 2020;7(4):233-236.
9. Ferrari R, Caram LM, Tanni SE, Godoy I. The relationship between vitamin D status and exacerbation in COPD patients – a literature review. Respir Med. 2018;139:34-38.
10. Alavi Foumani A, Mehrdad M, Jafarinezhad A, Ramezani E, Safarizadeh S. Impact of vitamin D on spirometry findings and quality of life in patients with chronic obstructive pulmonary disease: a randomized, double-blinded, placebo-controlled clinical trial. Int J Chron Obstruct Pulmon Dis. 2019:1495-1501.
11. Sharanjani MR, Nadi E, Vasheghani M, Moosazadeh M. The assessment of 25-hydroxy vitamin D serum level in asthmatic patients: A case-control study. Avicenna J Med Biochem. 2017;5(2):65-69.
12. Sluyter JD, Camargo CA Jr, Waayer D, Lawes CM, Toop L, Khaw KT, Scragg R. Effect of monthly, high-dose, long-term vitamin D on lung function: a randomized controlled trial. Nutrients. 2017;9(12):1353.
13. Burkes RM, Ceppe AS, Doerschuk CM, Couper D, Hoffman EA, Criner GJ, et al. Associations among 25-hydroxyvitamin D levels, lung function, and exacerbation outcomes in COPD: an analysis of the SPIROMICS cohort. Chest. 2020;157(4):856-865.
14. Manoli PG. A prospective study of clinical features and vitamin D levels in persistent asthmatics. Rajiv Gandhi University of Health Sciences (India). 2019.
15. Ghodrati S, Ezzatpanah A, Asadi-Khiavi M, Mohammadi H, Asghari A. Administration of vitamin D to ameliorate dyspnea of chronic obstructive pulmonary disease patients: a randomized controlled trial. Immunopathol Persa. 2019;5(2).
16. Clark K, Goldstein RL, Hart JE, Garshick E, Tun CG, Collins EG, et al. Plasma vitamin D, past chest illness, and risk of future chest illness in chronic spinal cord injury (SCI): a longitudinal observational study. Spinal Cord. 2020;58(4):504-512.
17. Maretzke F, Bechthold A, Egert S, Ernst JB, Melo van Lent D, Nießen M, et al. Role of vitamin D in preventing and treating selected extraskeletal diseases—an umbrella review. Nutrients. 2020;12(4): 969.
18. Ghosh AJ, Moll M, Hayden LP, Kenny A, Christiansen SC, Camargo CA Jr. Vitamin D deficiency is associated with respiratory symptoms and airway wall thickening in smokers with and without COPD: a prospective cohort study. BMC Pulm Med. 2020;20: 1-9.
19. Ahmad S, Arora S, Khan S, Jain S, Mathur P, Begum R. Vitamin D and its therapeutic relevance in pulmonary diseases. J Nutr Biochem. 2021;90:108571.
20. Arroyo-Díaz JA, Julve J, Vlacho B, Prieto-Montano P, Tarin N, Fortuny C. Previous vitamin D supplementation and morbidity and mortality outcomes in people hospitalised for COVID-19: a cross-sectional study. Front Public Health. 2021;9:758347.
21. Saleem A, Sharif S, Jarvis S, Moinuddin R. A comprehensive review on vitamin D as a novel therapeutic agent in chronic obstructive pulmonary disease. Cureus. 2021;13(2).
22. Jiménez D, Agustí A, Tabernero E, Lobo JL, Parra G, Barrios D, et al. Effect of a pulmonary embolism diagnostic strategy on clinical outcomes in patients hospitalized for COPD exacerbation: a randomized

clinical trial. JAMA. 2021;326(13):1277-1285.

23. Furulund E, Bemanian M, Berggren N, Strömberg C. Effects of nutritional interventions in individuals with chronic obstructive lung disease: a systematic review of randomized controlled trials. Int J Chron Obstruct Pulmon Dis. 2021:3145-3156.
24. Mathyssen C, Gayan-Ramirez G, Bouillon R, Janssens W. Vitamin D supplementation in respiratory diseases: evidence from randomized controlled trials. Pol Arch Intern Med. 2017;127(11):775-784.
25. Martineau AR, James WY, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2015;3(2):120-130.
26. Jorde I, Stegemann-Koniszewski S, Papra K, Röhling M, Mitterhuber L, Meibom K, et al. Association of serum vitamin D levels with disease severity, systemic inflammation, prior lung function loss and exacerbations in a cohort of patients with chronic obstructive pulmonary disease (COPD). J Thorac Dis. 2021;13(6):3597-3607.
27. Asbaghi O, Sadeghian M, Mozaffari-Khosravi H, Abbasnezhad A, Maleki V. The effect of vitamin D-calcium co-supplementation on inflammatory biomarkers: a systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020;129: 155050.
28. Camargo CA Jr, Toop L, Sluyter JD, Lawes CM, Scragg R. Effect of monthly vitamin D supplementation on preventing exacerbations of asthma or chronic obstructive pulmonary disease in older adults: post hoc analysis of a randomized controlled trial. Nutrients. 2021;13(2):521.
29. Jolliffe DA, Camargo CA Jr, Sluyter JD, Martineau AR, Ginde AA, Giovannucci EL, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. Lancet Diabetes Endocrinol. 2021;9(5):276-292.
30. Chałubi ski M, Kowalski ML. Lifetime prevention of chronic airway diseases. In: Prevention of chronic diseases and age-related disability. Elsevier; 2019: 83-90.
31. Callejo M, Mondejar-Parreño G, Esquivel-Ruiz S, de Frutos S, Pérez-Vizcaíno F, Cogolludo AL. Total, bioavailable, and free vitamin D levels and their prognostic value in pulmonary arterial hypertension. J Clin Med. 2020;9(2):448.