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The Association of Serum Vitamin D Levels with Lung Function, Symptom Severity, and Exacerbations in Stable COPD Patients

Nurrahmah Yusuf*, Chelsy Mekasari, Sri Dianova, Herry Priyanto, Budi Yanti

Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
*Corresponding author: rahmah_ys@yahoo.com

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a significant health burden associated with a decrease in quality of life. Patients with the disease often have a deficiency of Vitamin D, a fat-soluble vitamin important for respiratory health. A previous study suggested an association between low vitamin D levels and poor lung function, as well as increased exacerbation, and more severe COPD symptom. Therefore, this study aimed to assess serum vitamin D levels in stable COPD patients and explore association with lung function, symptom severity, and frequency of exacerbation. **Methods**: This was a cross-sectional study conducted from May to July 2023 at Lung Polyclinic of Dr. Zainoel Abidin Regional General Hospital (RSUDZA) Banda Aceh. A total of 30 subjects selected based on specific inclusion and exclusion criteria were included. **Results**: The results showed that the mean serum vitamin D level was 26.25 ng/mL, with 56.7% of subjects showing vitamin D insufficiency. Statistical analysis showed p-values of 0.577, 0.637, 0.120, and 0.135 for lung function, exacerbation, COPD Assessment Test (CAT), and Modified Medical Research Council (mMRC) dyspnoea scale respectively, indicating no significant association between vitamin D levels and these outcomes. Potential confounding factors include unassessed variables such as medication use, educational background, and psychological status. Conclusion: This study found no significant association between serum vitamin D levels and lung function, symptom severity, and frequency of exacerbation in stable COPD patients. Further studies with a larger sample size and extended follow-up are needed to confirm these results and explore additional influencing factors.

Keywords: COPD, Lung Function, Vitamin D Deficiency

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptom and airflow limitation caused by airway and/or alveolar abnormalities. This chronic disease has a substantial impact on patient's quality of life and progresses slowly. An elevated chronic inflammatory response of the airways caused by specific irritating gases or particles is associated with COPD (Soeroto and Suryadinata, 2014; Aggarwal, 2022).

COPD can be prevented and treated but is among the diseases with the highest health burden. Global Initiative for Chronic Obstructive Lung Disease (GOLD) reports that health costs account for 56% of the total paid for respiratory diseases. COPD has high mortality and morbidity throughout the world (Soeroto and Suryadinata, 2014). According to World Health Organization (WHO) data, it is included in the top four non-communicable diseases that have a high mortality rate after cardiovascular disease, cancer, and diabetes. The latest global observation data in 2015 states that COPD is ranked third as the main cause of death in the world. Approximately 5% of all Global deaths are caused by the disease with 3.17 million deaths (Lowe et al., 2019; Fernández et al., 2020).

The hallmark of stable COPD is variable degrees of inflammation in the alveoli as well as large and small airways, leading to mucus hypersecretion, airway constriction, and alveolar destruction. Symptom that arise in patients

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with stable COPD can shift to acute exacerbation and increase the incidence of death. Increased severity will further reduce the quality of life. An acute worsening of COPD known as an acute exacerbation necessitates further treatment, negatively affects health, and accelerates the course of the disease. Respiratory tract infections are one of the most common causes of exacerbation, although there are other causes. Narrowing of the airways and excessive mucus production leads to decreased lung function and results in an increased incidence of respiratory failure (Fatimah, Soemarwoto, and Karima, 2019)

The respiratory system greatly benefits from vitamin D and patients with COPD frequently have deficiency. Lung function can be disrupted by low vitamin D levels, particularly in patients with coexisting respiratory conditions in the past. Male COPD patients have a high incidence of deficiency, according to recent studies. Furthermore, low levels of vitamin D have been connected to reduced severity of COPD, frequency of exacerbation, and forced expiratory volume in one second (FEV1) (Soeroto et al., 2021).

COPD assessment aims to ascertain the degree of airflow restriction, the effect on the state of health, and the prognosis for upcoming events, including hospitalizations, exacerbation, and death. When estimating significant clinical outcomes for COPD patients, such as death and hospitalizations, or deciding the possibility of non-pharmacological therapy, FEV1 must be considered at the population level. Acute exacerbation and decreased lung function are linked to vitamin D deficiency, which is frequently the cause of symptom in COPD patients (Fatimah, Soemarwoto, and Karima, 2019; Aggarwal, 2022)

Patients frequently have vitamin D deficiency but is still unclear whether vitamin D concentration and the risk of COPD exacerbation are consistently associated. Three studies found no effect and one reported vitamin D had a protective effect on the risk of exacerbation, according to four double-blind randomized control trials. Vitamin D supplementation was found to have no effect in patients experiencing moderate to severe COPD exacerbation, but it clinically and statistically had a significant protective effect at concentrations less than 25 nmol/L (Jolliffe et al., 2019). Therefore, this study aimed to investigate the association between serum vitamin D levels and lung function, symptom assessment, and number of exacerbations in patients with stable COPD.

Method

This cross-sectional study was conducted among stable COPD patients treated at RSUDZA, Banda Aceh. Inclusion criteria were patients aged ≥ 40, diagnosed with COPD based on anamnesis, physical exam, and spirometry assessment after administration of bronchodilator based on GOLD criteria (FEV1/FVC). Meanwhile, exclusion criteria were patients with acute exacerbation COPD, had comorbidity that can affect the metabolism of vitamin D (e.g., Diabetes mellitus, Asthma, chronic kidney disease, chronic liver disease), had malabsorption syndrome (chron's disease, inflammatory bowel syndrome, gastrectomy or Jejunoileostomy) and vitamin D supplementation in the last 3 months. This study used primary data from serum vitamin D levels as well as past medical history and secondary data from records to collect information on patient characteristics.

Data collection started from May – July 2023 using questionnaire data and interviews conducted physically face to face. After data collection was carried out, 30 patients with stable COPD who met the study criteria were included as subjects.

Vitamin D levels in patients with stable COPD were obtained by examination in the laboratory using a venepuncture procedure in the cubital fossa with an aseptic technique. About 3 ccs of blood were collected and the measurement was carried out using the Enzyme-linked immunosorbent assay (ELISA). The blood samples were taken by laboratory staff of a private laboratory in, Banda Aceh based on a memorandum of cooperation with the clinic. The results of vitamin D levels were categorized as sufficient (> 30 ng/mL), insufficient (20-30 ng/mL), and deficient (< 20 ng/mL).

Lung function was obtained by spirometry examination in the form of FEV1. Based on the results, subjects were grouped into four GOLD groups, namely GOLD 1, GOLD 2, GOLD 3 and GOLD 4. Symptom assessment was conducted using CAT and mMRC questionnaires. Furthermore, mMRC is the sum of the scores obtained from subjects based on questionnaires submitted to assess the severity of shortness of breath. There are five points (0-4) based on the severity of dyspnea. The mMRC scale is divided into two categories, namely mMRC with a value of 0-1 (mild symptom) and ≥ 2 (severe symptom). The CAT score consists of two categories, namely CAT < 10 (mild symptom) and ≥ 10 (severe symptom). This score was obtained during an interview using the CAT questionnaire.

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Exacerbation assessed by anamnesis results include severe shortness of breath, productive cough, and purulent sputum. The number of exacerbation recurrences was calculated in the last 1 year and categorized into 0–1 (non-exacerbation) and ≥ 2 (exacerbation).

Table 1. Socio-demographic characteristics of study participants

Characteristic	Frequency (n=30)	Percentage (%)
Gender		
Male	26	86,7
Female	4	13,3
Marrital Status		
Married	30	100
Allergy history		
No	25	83,3
Yes	5	16,7
Alcohol history		
No	23	76,7
Yes	7	23,3
Smoking History		
No	4	13,3
Yes	26	86,7
Brinkman Index, ***median : 720 (0 - 3200)***		
None	4	13,33
Mild	2	6,67
Moderate	3	10
Severe	21	70
Age, ***mean±SD (66 ± 7,73)***		
45-59	5	16,67
60-69	16	53,33
≥ 70	9	30
BMI, ***mean±SD (22,47 ± 4,42)***		
< 18,5	6	20
18,5-24,9	18	60
25,0-29,9	4	13,33
≥ 30	2	6,67
Job		
Civil servant	1	3,3
Private employee	1	3,3
Retirees	13	43,3
Labourer	8	26,7
Farmer	6	20
Housewives	1	3,3
Education		
Primary school	9	30
Junior Highschool	5	16,7
Senior Highschool	7	23,3
Diploma	3	10
Bachelor	6	20

SPSS was then used to examine the data while univariate analysis was used to analyse frequency distribution, proportion of variables, and sample characteristics. Bivariate analysis was used to assess the correlation between serum vitamin D level, lung function (FEV1) and the number of exacerbations.

Results

It was found that most subjects were male (86.7%), had no history of allergies (83.3%), and had no history of consuming alcohol (76.7%). The youngest was 45 years old and the oldest was 78 years old, with a mean age of

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66 years. The mean Body Mass Index (BMI) was 22.47 or in the normal category. Regarding occupation, some of the subjects were retirees (43.3%) others were in the labour profession (26.7%), while some were farmers (20%). The education level was mostly elementary school (30%) and detailed characteristics of the subjects are presented in Table 1.

It was found that 23.3% of patients had normal serum vitamin D levels (sufficiency), 56.7% had insufficiency, and 20% had deficiencies.The FEV1 values for lung function were classified into four categories: mild (≥ 80%), moderate (50-79.9%), severe (30-49.9%), and very severe, with 26.7%, 36.7%, 36.7%, and 0 subjects in each category, respectively. Furthermore, the majority were in category GOLD 2 and 3, which included 11 subjects each (36.7%). COPD grouping based on GOLD ABE assessment tools was also conducted, showing two groups namely B and E. A total of 20 subjects (66, 7%) were in Group B, and the other 33.3% were in E with a total of 10 subjects. Detail of Physical assessment, Laboratory, and spirometry result can be found in Table 2.

Tabel. 2 Physical assessment, Laboratory, and spirometry results

Examination	Frequency (n)	Percentage
Vitamin D Status		
Deficiency	6	20
Insufficiency	17	56,7
Sufficiency	7	23,3
FEV_1		
≥ 80 %	8	26,7
50-79,9%	11	36,7
30-49,9%	11	36,7
GOLD Classification		
GOLD 1	8	26,7
GOLD 2	11	36,7
GOLD 3	11	36,7
CAT Score		
Oct-15	11	36,67
16-20	10	33,33
21-25	6	20
26-30	2	6,67
>30	1	3,33
Group COPD based on GOLD ABE assessment tools		
Grup B	20	66,7
Grup E	10	33,3
mMRC scale		
1	1	3,33
2	7	23,33
3	19	63,34
4	3	10
Exacerbation		
0	16	53,33
1	9	30
2	5	16,67

Interviews were conducted to assess symptom of the subjects and the results showed that all 30 had severe symptom or CAT ≥ 10. The highest number of subjects with a CAT score of 10-15 was 11 (36.37%) then followed by those with a score of 16-20, namely 10 people (33.33%). Meanwhile, only 1 subject (3.33%) had a score > 30 (CAT score = 35). For mMRC assessment, 1 subject had mild symptom (mMRC = 1) and 29 others had severe

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symptom or in the percentage of 3.33% and 96.67% respectively. The majority obtained mMRCs score of 3 (19 subjects; 63.34%). Furthermore, a significant proportion of subjects did not experience exacerbation (25; 83,33%). Among the 25 subjects who did not experience exacerbation, 16 (53.33%) had a value = 0. Meanwhile for the other 9 subjects (30%) the value = 1.

Subjects with sufficient vitamin D levels had lung function at GOLD 3 (42.86%). Meanwhile, those with insufficient vitamin D levels had lung function at GOLD 3 and 2 (41.18%) and the majority with vitamin D deficiency were in GOLD 1 group (50,0%). No association between serum vitamin D levels and Gold classification in stable COPD subjects was found. Furthemore, all subjects (100%) had a CAT score ≥ 10 and there was no CAT < 10. The analysis showed no significant correlation between serum vitamin D levels and CAT(p = 0,12). Subjects in the mMRC ≥ 2 or severe symptom group had vitamin D insufficiency and sufficiency levels of 100% respectively. Meanwhile, for subjects with vitamin D deficiency levels, it was 83.33%. No statistically significant difference between mMRC score and Vitamin D status was found.

Table 3. Association of serum Vitamin D level toward Lung Function, Symptom Assessment, and Number of Exacerbation of patients with Stable COPD

Variable	Vitamin D Status								X^2	*P-value*
	Deficiency		Insufficiency		Sufficiency		Total			
	n	%	n	%	n	%	n	%		
Pulmonary Function										
GOLD 1	3	50,0	3	17,65	2	28,57	8	26,67	2.8	0,58
GOLD 2	2	33,33	7	41,18	2	28,57	11	36,67		
GOLD 3	1	16,67	7	41,18	3	42,86	11	36,67		
mMRC scale										
0-1	1	16,7	0	0,0	0	0,0	1	3,3	4,1	0,12
≥2	5	83,33	17	100,0	7	100,0	29	96,67		
Exacerbation										
No	5	83,33	14	82,35	6	85,71	25	83,33	0,04	0,98
Yes	1	16,67	3	17,65	1	14,29	5	16,67		

Exacerbation was found in 17.65% of subjects showing Vitamin D insufficiency, 16,6% of those with deficiency levels, and 14.29% of subjects who had sufficiency status. The analysis results also showed no association between vitamin D status and exacerbation. Detail of the association of serum Vitamin D level toward lung function, ymptom assessment, and number of exacerbation of patients with stable COPD is presented in Table 3.

Discussion

Despite the availability of prevention and treatment measures, COPD is among the diseases with the highest health burden. GOLD reports that medical costs due to COPD account for approximately 56% of the total costs paid for respiratory diseases. This disease has high mortality and morbidity throughout the world (Soeroto and Suryadinata, 2014). According to WHO data, COPD is included in the top four non-communicable diseases which have a high mortality rate after cardiovascular disease, cancer, and diabetes. The observation data in 2015 states that the disease is ranked third as the main cause of death in the world, accounting for 5% or 3.17 million deaths globally (Fernández et al., 2020). This study aims to discover correlation between vitamin D levels with lung function and the quality of life in stable COPD patients. Serum vitamin D levels were measured and the relationships with lung function, symptom assessment, and the frequency of exacerbation were investigated in patients with stable COPD.

After data collection was carried out, a total of 30 stable COPD patients who met the inclusion criteria participated as subjects. Selected subjects received an explanation regarding the aims and benefits of the study and were asked to sign an agreement. A 3cc vein puncture procedure was performed in the cubital fossa using an aseptic technique to determine serum vitamin D levels through the Enzyme-linked immunosorbent assay (ELISA). Subsequently, FEV1 assessment was carried out using spirometry. The frequency of exacerbation within 1 year was determined through patient's history. Symptom assessment was carried out using the CAT and mMRC checklists, then all data obtained were tabulated for further processing and analysis.

The subjects had a mean age of 66 years and BMI within normal limits. Easter et al (2020) reported that aging negatively impacted the structure and function of lungs (Easter et al., 2020). Age-associated diseases arise from persistent low-grade inflammation and increased reactive oxygen species (ROS) causing damage that cannot be prevented by physiological antioxidant and anti-inflammatory mechanisms (Easter et al., 2020). When coupled

with other common risk factors for COPD, such as smoking, the failure of physiological anti-inflammatory and antioxidant mechanisms in the elderly potentially leads to cell and/or tissue damage and COPD (Easter et al., 2020). These risk factors are also in accordance with the characteristics of most subjects (86.7%) who were smokers and had a mean Brinkman index of 720.

The subjects were predominantly males, including 26 (86.7%), with only 4 females (13.3%). A meta-analysis of 156 studies worldwide by Ntritsos et al (2018) found that the prevalence of COPD was 9.23% in males and 6.16% in females. When the analysis was restricted to subjects aged 40 years or older, the prevalence increased to 11.55% in men and 7.47% in women (Ntritsos et al., 2018). Meanwhile, in Indonesia, Riskesdas data in 2013 showed COPD prevalence of 3.7% with males having a greater value of 4.2% than females at 3.3% (Kemenkes, 2013).

BMI of the subjects was within normal limits and according to Huber et al. (2020), BMI and health-related quality of life (HRQoL) in COPD patients have a non-linear relationship. After losing weight, the HRQoL of patients with mild to severe COPD may improve. BMI between 30–40 is not associated with a worsening of subjective complaints for very severe COPD. Therefore, unless there are other medical indications, this metric is not the primary goal of treatment (Huber et al., 2020) Another study by Wu et al. (2018) found that although lung function improved with rising BMI, inflammation levels and exacerbation frequency decreased (Wu et al., 2018).

Referring to vitamin D status, about 23.33% showed normal serum levels (sufficiency), 56.67% had insufficiency and 20% had deficiencies. According to the Indonesian Ministry of Health, serum vitamin D can be categorized as sufficiency (> 30 ng/mL), insufficiency (20-30 ng/mL), and deficiency (< 20 ng/mL). This value is slightly higher (geographic impact) compared to WHO which defines vitamin D insufficiency as serum 25-hydroxyvitamin D [25(OH)D] below 20 ng/ml (50 nmol/liter) (Gallagher and Sai, 2010). The US Institute of Medicine (IOM) categorizes 25(OH)D as deficiency, (< 12 ng/ml), insufficiency (12–20 ng/ml), and adequate (20–50 ng/ml) (Divakar et al., 2020). Normal vitamin D levels in this study were caused by the large amount of sunlight exposure that the subjects received when carrying out daily routines. Some of the subjects were retirees, but currently engaged in gardening activities to fill free time. Apart from sun exposure, the high levels of vitamin D were also due to the amount of intake from consuming fish.

Divakar et al., (2020) examined the prevalence of vitamin D deficiency among indoor workers in Singapore. The results showed the mean serum vitamin D concentration of the subjects was under the optimal level and a third were classified as deficient (Divakar et al., 2020). Office and workshop workers as well as night shift workers had a high risk of experiencing deficiency (Divakar et al., 2020). According to Nimitphong et al (2013), vitamin D deficiency in the Southeast Asia population is more prevalent than expected ranging from between 6-70%. Skin pigmentation, aging, sun protective behavior such as sunscreen use, religion, lifestyle, and dietary variances are all factors that influence vitamin D levels. Advanced age is also a risk factor for vitamin D insufficiency. However, the elderly population in Thailand had higher levels of 25(OH)D than young people (Nimitphong and Holick, 2013).

The mean serum vitamin D level was 26.25 ng/mL and FEV1 was 54.55. Statistically, there was no significant correlation between serum vitamin D levels and FEV1 (p=0.577). A previous study assessed the relationship between serum vitamin D levels and FEV1 in patients with stable COPD in Indonesia (Soeroto et al., 2021). A total of 30 subjects had a mean age of 62 years and vitamin D of 20.17 ng/mL with 50% having low levels (<20ng/mL). Furthermore, there was no significant correlation between vitamin D levels and VEP1 (Soeroto et al., 2021). In terms of subject characteristics, both studies have similarities, including being conducted in Indonesia, and the majority of the sample had advanced age and a similar sample size.

Janssens et al (2010) found a significant correlation between two factors, namely vitamin D deficiency and disease severity measured by FEV1.(Janssens et al., 2010). Another study by Zendedel et al (2015) found that vitamin D intake improved FEV1 in patients with severe and very severe COPD (Zendedel et al., 2015). The absence of a significant correlation between serum vitamin D levels and FEV1 could be attributed to several variables. This study did not examine various variables that influence lung function measured by FEV1, such as treatment, drug type, and treatment duration. (Soeroto et al., 2021).

The association between serum vitamin D levels and COPD assessment test (CAT) in patients with stable COPD in Indonesia was assessed by Soeroto et al (2021). The results showed that vitamin D levels were negatively correlated with CAT scores, suggesting low vitamin D levels were associated with increasing CAT scores (Soeroto et al., 2021). Similarly, Baran et al (2017) found a relationship between increased CAT and vitamin D deficiency (Baran, 2017). On the other hand, our study fails to prove such association between serum vitamin D levels and symptom assessment using CAT scores and mMRC values. Possible causal factors are differences in perception, knowledge, and also the psychological status of subjects.

Furthermore, we found that the mean serum vitamin D level in COPD group B group was slightly lower than in group E with a mean difference of 0.79 ng/mL. Statistically, there was no difference in serum vitamin D levels based on symptom severity groups ($p > 0.05$). We also assessed the relationship between serum vitamin D levels and the number of exacerbation. Although the correlation between serum vitamin D levels and the number of exacerbation was not statistically significant, the coefficient value was very weak and negative. This implies that an increase in serum vitamin D levels is inversely proportional to the number of exacerbation.

Soeroto et al., (2021) found that vitamin D levels were negatively correlated with the number of exacerbation. This implied that low levels of vitamin D were associated with more frequent exacerbation (Soeroto et al., 2021). Another study by Zendedel et al (2015) found that vitamin D intake reduced exacerbation in patients with severe and very severe COPD (Zendedel et al., 2015). Further research should explore the potential benefits of vitamin D supplementation in reducing exacerbation frequency in COPD patients, particularly given the evidence indicating a possible inverse relationship between vitamin D levels and exacerbations. This study had a small sample size and a short period of follow-up, leading to a statistically insignificant correlation between variables. Other factors that could contribute to this result were confounding factors such as treatment, type of drug used, and duration of treatment.

In conclusion, there was no correlation between serum vitamin D levels and lung function, symptom assessment, and number of exacerbations in patients with stable COPD. More studies are needed, ideally with a bigger sample size and a longer follow-up period.

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Conflict of Interest

The authors declare that there is no conflict of interest

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