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Original Article

The Effect of Vitamin D Deficiency in Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVE: It has been suggested that Vitamin D Deficiency (VDD) worsens lung functions and COPD lowers vitamin D levels, but this has not been proven yet.

MATERIAL AND METHODS: The study was carried out between January 2014 and September 2015. All the COPD patients with 25 (OH) D3 measurements were included in this study. The patients < 40-year-old, or with a smoking history of less than 10 package-year, or with asthma, bronchiectasis, pneumonia, tuberculosis, cancer, were excluded from the study. Medical records about age, gender, pulmonary function test, body mass index (BMI), annual exacerbations/hospitalizations, modified British Medical Research Council (mMRC) level and serum 25 (OH) D3 were obtained.

RESULTS: The data of 216 (83.8% male) patients were examined in the study. The mean age was 66.88 ± 10.3 years. The mean vitamin D level was 21.1 ± 13.73 ng/mL. Of the patients, 57.9% had VDD, and even 19.9% were in severe VDD. Only 26.4% had adequate vitamin D level. There was a significant in BMI, FEV1, FVC, annual exacerbation and hospitalisations between the patients with vitamin D levels > 20 ng / mL and ≤ 20 ng / mL. Vitamin D level of patients with mMRC level 1 was significantly higher than those with mMRC 2, 3, 4 (respectively $P = .03$; $P = .026$; $P = .014$).

CONCLUSION: In this study, we found that lung function was worse in COPD patients with VDD and VDD increased with increasing severity of COPD.

KEYWORDS: COPD, forced expiratory volume in 1 second, forced vital capacity, vitamin D, exacerbation
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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive and persistent airflow restriction and is caused by chronic exposure of individuals with a genetic predisposition to cigarette smoke and/or other environmental factors.[1] It is one of the major fatal diseases, and it is predicted by World Health Organization (WHO) that it would be the third cause of death in 2030, just after ischemic heart disease and cerebrovascular disease.

Vitamin D is a kind of steroid hormone that plays an important role in bone metabolism and neuromuscular functions. Vitamin D deficiency (VDD) has also been associated with decreased lung function, increased inflammation, and decreased immunity.[2-5] COPD poses a high risk for VDD, which is thought to be caused by malnutrition, insufficient outdoor activity, kidney dysfunction, and high catabolism associated with steroid therapy. On the other hand, VDD is also supposed to adversely affect pulmonary functions because, for optimal lung function, vitamin D seems required, beginning from the developmental stages. In a manner of speaking, COPD patients are in a vicious circle of worse lung function due to VDD and decreased vitamin D level due to COPD.

The present study aimed to assess the vitamin D levels in COPD patients and its relationship with symptom score, lung function, severity of COPD, risk of exacerbations, and hospitalizations due to COPD exacerbation.

MATERIAL AND METHODS

The data of all the patients who applied to our COPD outpatient clinic were obtained from the electronic hospital data system retrospectively. The inclusion and exclusion criteria were created by considering the factors that might have an effect on vitamin D level (Table 1). All the patients had COPD and were the ones whose vitamin D level had been analyzed for any reason in the last 1 year.

The data about the patient's age, gender, pulmonary function test, smoking history, body mass index (BMI), drugs, COPD exacerbations, hospitalizations in last year due to COPD exacerbations, modified British Medical Research Council (mMRC) level, serum 25 (OH) D3, C-reactive protein (CRP), leukocyte and sedimentation results were obtained from the patient's electronic files. The data were analyzed by an appropriate statistical method.

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Table 1. The Inclusion and Exclusion Criteria for the Patients

Inclusion Criteria	Exclusion Criteria
• ≥40 years old • ≥10 packet year smoking history • 25 (OH) D3 analyzed in last one year • COPD according to GOLD guideline (dyspnea, chronic cough or sputum, history of exposure to risk factors such as cigarette or noxious gas and post-bronchodilator FEV1/FVC <0.70)	• Comorbidities • (asthma, bronchiectasis, pneumonia, tuberculosis, cancer, parathyroid disease)

25 (OH) D3, 25-hidroksi-vitamin D; COPD, chronic obstructive pulmonary disease; GOLD, global initiative for chronic obstructive lung disease; FEV1/FVC, forced expiratory volume in one second/forced vital capacity.

Functional dyspnea burden was evaluated by mMRC. For the evaluation of airflow obstruction severity, the global initiative for chronic obstructive lung disease (GOLD) staging system and for the assessment of COPD, the "ABCD" combined assessment tool of the GOLD guideline in 2015 was used. Vitamin D status was categorized according to the vitamin D levels, like that, serum 25(OH)D3 ≥ 30 ng/mL adequate, serum 25(OH)D3 between 29 and 21 ng/mL insufficient, serum 25(OH)D3 between 20 and 10 ng/mL deficient, serum 25(OH)D3 < 10 ng/mL severe deficient.

The study protocol was approved by Ethical Committee (70904504/364). The approval allowed retrospective data collection and reporting of anonymous results without the acquisition of informed consent from eligible study subjects.

Statistical Analysis

The Statistical Package for Social Sciences version 21.0 software (IBM Corp.; Armonk, NY, USA) was used for the analysis. $P < .05$ was considered statistically significant. Descriptive statistics were presented with frequency, percentage, mean, standard deviation (SD), median, minimum (min), and maximum (max) values. Fisher's exact test or Pearson chi-square test was used to analyze the relationships between categorical variables. For the distribution of numerical measurements, Kolmogorv–Smirnov, for comparison of the group's *t*-test, Mann–Whitney *U*-test, ANOVA, and Sidak test were used.

RESULTS

Two hundred sixteen patients (181 male), aged between 41 and 89 (mean age 66.88 ± 10.3) were evaluated in the study. The average cigarette consumption was 41.2 ± 26 pack-years and 32 (14.8%) of the patients were current smokers. According to COPD GOLD stages, the distribution of patients was 3.7% for stage I, 44.98% for stage II, 38.4% for stage III, and 13% for stage IV. Most of the patients were in GOLD B (45.4%), and 51 (23.6%) patients were in GOLD D. A total of 147 (68.1%) patients were on inhaler corticosteroid (ICS) treatment, and only 5 (2.3%) of the patients had low body weight. The mean level of vitamin D was 21.1 ± 13.73 ng/mL (range, 3-81). Of the patients overall, 82 (38%) patients had VDD, 43 (19.9%) patients had severe VDD, while 57 (26.4%) patients had adequate vitamin D level. Patients characteristics are summarized in Table 2.

There was no significant difference between vitamin D levels (adequate-insufficient-deficient-severe deficient) in respect to gender ($P = .069$) and BMI ($P = .08$). The mean forced expiratory volume in 1 second (FEV1 L) and forced vital capacity (FVC L) levels of the patients with VDD were lower than those without VDD ($P = .009$; $P = .015$). The mean exacerbation and hospitalization in patients without VDD was significantly lesser than in patients with VDD ($P = .015$; $P = .018$). CRP, leukocyte, and sedimentation rates were significantly higher in patients with VDD than those without VDD ($P = .013$; $P = .03$; $P = .024$). The distribution of mean values of FEV1, FVC, exacerbation, hospitalization, CRP, sedimentation rate, and leukocyte according to vitamin D status is summarized in Table 3.

The vitamin D level decreased gradually as the dyspnea score increased. Vitamin D level of patients with mMRC level 1 was significantly higher than those with mMRC 2, 3, 4 ($P = .03$; $P = .026$; $P = 014$). Vitamin D level was significantly higher in GOLD A than GOLD B, C, and D ($P = .03$; $P = .01$; $P = .01$). The distribution of mean vitamin D levels according to mMRC levels and GOLD groups is summarized in Table 4.

DISCUSSION

Our study is one of the studies evaluating the vitamin D levels of COPD patients and the relationship between the vitamin D status and COPD stages, lung function, dyspnea scale, exacerbation, and hospitalization. We found that the prevalence of VDD and vitamin D insufficiency was very high among COPD patients. Furthermore, VDD was associated with pulmonary function tests, especially FEV1 and FVC. Moreover, we observed that, COPD patients with VDD, had a higher mMRC. In addition to that, we found that exacerbation and hospitalization were more frequent in COPD patients with VDD. Our findings show that VDD was associated with the worsening dyspnea score, the increased COPD severity, and

Main Points

- In our study, we observed that only 26.4% of patients with COPD had sufficient vitamin D levels and vitamin D insufficiency and deficiency were common in COPD.
- There was a significant difference in BMI, FEV1, FVC, exacerbations, and COPD-related hospitalizations between the patients with vitamin D levels > 20 ng / mL and ≤ 20 ng / mL.
- Vitamin D levels were also associated with COPD severity. As the severity of COPD increased, so did the severity of vitamin D deficiency.

Table 2. Patients Characteristics

	Patients, *N* (%)
Stage	
I	8 (3.7%)
II	97 (44.9%)
II	83 (38.4%)
IV	28 (13%)
GOLD	
A	64 (29.6%)
B	98 (45.4%)
C	3 (1.4%)
D	51 (23.6%)
mMRC	
0	-
1	59 (27.3%)
2	98 (45.4%)
3	55 (25.5%)
4	4 (1.9%)
Cigarette	
Current smoker	32 (14.8%)
Ex-smoker	184 (85.2%)
BMI (kg/m^2)	
<18.5	5 (2.3%)
18.5-24.9	90 (41.7%)
25-29.9	75 (34.7%)
≥30	40 (18.5%)
≥40	6 (2.8%)
Drugs Medications with ICS	147 (68.05%)
Medications with others than ICS	69 (31.95%)
Vitamin D status	
Adequate	57 (26.4%)
Insufficient	34 (15.7%)
Deficient	82 (38%)
Severe deficient	43 (19.9%)

GOLD, global initiative for chronic obstructive lung disease; mMRC, modified British Medical Research Council; ICS, inhaler corticosteroid; BMI, body mass index.

more frequent adverse COPD outcomes, such as exacerbation and hospitalization.

VDD is a common health problem all over the world. About one-third of the population has VDD in the USA, ranging from 40 to 100% among European elders.[6-8] In research about the prevalence of VDD in Turkish people, it was observed that the mean level of vitamin D in people above 40 years old, was 22.1 ± 23.7 ng/mL (range, 3-180) and inadequate (<24 ng/mL) vitamin D prevalence was about 69%.[9] This endemic problem seems to be even more frequent and worse in COPD patients. In a study, it was found that COPD patients had a substantially lower vitamin D level, even 27% had less than 4-5 ng/mL vitamin D.[10] In another study, it was shown that there was a statistically significant inverse association between vitamin D status and COPD.[11] Moreover, a recent meta-analysis of the studies about vitamin D and COPD reported that the serum vitamin D levels in COPD patients were lower than the levels in control subjects.[12] In our study, the mean level of vitamin D was 21.1 ± 13.73 ng/mL (range, 3-81), and inadequate (<20 ng/mL) vitamin D prevalence was about 75%. By these results, it can be interpreted that VDD is a more common problem in COPD patients than in healthy people.

Low vitamin D level is suggested to be a risk factor for worse lung function based on previous mouse experiments.[13,14] Black et al. found in an epidemiological study in healthy subjects that there is a graded relationship between serum vitamin D level and lung function. Patients with vitamin D ≤ 16.2 ng/mL had a mean FEV1 that was 126 mL lower than the mean FEV1 of the patients with vitamin D ≥ 34.3 ng/mL.[15] Similarly, a significant correlation between the vitamin D levels and FEV1 in COPD patients also, was observed in another research.[2] Later, discordant with the previous studies, Shaheen et al.[16] reported that they did not find a positive association between serum vitamin D and adult lung function. Furthermore, in a 6-year follow-up case–control study, it was observed that baseline vitamin D level was not predictive of subsequent lung function decline.[17] Our study revealed a negative relationship between vitamin D level and lung function. The mean FEV1 and FVC level was lower in COPD patients with VDD, and the vitamin D level decreased as COPD stage increased. Similar to ours, in a recent study, FEV1 was lower in subjects with VDD.[18] In summary, some studies have shown an inverse relationship between lung function and vitamin D levels in COPD patients, while others have not. So, the relationship between vitamin D and lung function is still unclear.

A substantial number of COPD patients suffer from exacerbations, which is usually triggered by infections. An antimicrobial peptide, cathelicidin (LL-37), expressed in secretory granules of many cells in the airways, is suggested to be effective in killing antibiotic resistant strains, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, Chlamydia, and various viruses.[19] The activity of the genes encoding LL-37 is regulated by promoter regions containing vitamin D receptors, so when the vitamin D is deficient, LL-37 level is decreased. Based on this, the bacterial load in the airway and therefore the risk of COPD exacerbation is supposed to be increased in the case of VDD. In the subsequent analysis of the COPD Gene Study, VDD was found to be associated with an increased frequency of severe exacerbations.[18] In our study, we found that VDD patients had higher exacerbations and hospitalizations than those without VDD. In a randomized, double-blind, placebo-controlled trial of vitamin D3 supplementation in COPD patients, it was observed that vitamin D3 supplementation protected against moderate or severe exacerbation, and that finding suggests that correction of VDD in COPD patients reduces the risk of moderate or severe exacerbation.[20] Furthermore, in another double-blind, placebo-controlled, randomized clinical trial, vitamin D intake (100 000 IU per 4 weeks for 6 months) improved COPD exacerbation, regardless of whether the patients had VDD

Table 3. The Mean Values of FEV1, FVC, Exacerbation, Hospitalization, CRP, Sedimentation, and Leukocyte According to Vitamin D Status

	Non-VDD (>20 ng/mL)		VDD (≤20 ng/mL)		
	Adequate	**Insufficient**	**Deficient**	**Severe deficient**	***P***
Gender (*n*)					
Male	50	47	45	39	.069
Female	10	8	9	8	
BMI	26.22 ± 5.48	24.66 ± 2.4	22.82 ± 4.6	22.24 ± 4.8	.08
FEV1 L, (mean ± SD)	1.78 ± 0.56	1.45 ± 0.55	1.26 ± 0.41	1.01 ± 0.42	.009
FEV1(%), (mean ± SD)	59.6 ± 15.2	52.6 ± 17.8	47.1 ± 14.4	40.2 ± 14.6	.019
FVC L, (mean ± SD)	2.63 ± 0.81	2.25 ± 0.74	1.92 ± 0.62	1.66 ± 0.68	.015
FVC (%), (mean ± SD)	70.6 ± 17.9	63.6 ± 17.6	56.2 ± 15.6	50.4 ± 15.0	.045
FEV1/FVC, (mean ± SD)	64.1 ± 4.9	62.2 ± 6.1	62.8 ± 6.4	59.1 ± 8.3	.02
Exacerbations, (mean ± SD)	0.41 ± 0.16	0.99 ± 0.56	1.04 ± 0.78	1.60 ± 1.38	.015
Hospitalization, (mean ± SD)	0.25 ± 0.07	0.82 ± 0.41	0.86 ± 0.51	1.26 ± 1.28	.018
CRP, (mean ± SD)	1.0 ± 0.53	1.4 ± 0.41	2.4 ± 0.44	4.1 ± 0.78	.013
Sedimentation, (mean ± SD)	10.91 ± 2.0	16.94 ± 2.2	19.09 ± 1.5	23.28 ± 2.5	.024
Leucocyte, (mean ± SD)	7671 ± 214	8603 ± 397	10035 ± 344	10900 ± 741	.03

VDD, vitamin D deficiency; BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CRP, C-reactive protein.

Table 4. The Distribution of Mean Vitamin D Levels According to mMRC Levels and GOLD Groups

	mMRC				GOLD group			
	1	**2**	**3**	**4**	**A**	**B**	**C**	**D**
Vitamin D (25(OH)D3)	32.9 ± 14.39	18.8 ± 11.34	13.08 ± 7.71	12.6 ± 8.55	32.8 ± 14.32	17.9 ± 9.77	15.6 ± 11.5	12.77 ± 9.69

mMRC, modified British Medical Research Council; GOLD, global initiative for chronic obstructive lung disease.

or not.[21] Moreover, it was observed that, the mean number of severe exacerbation in COPD subjects with severe VDD was significantly higher, during the 7-year follow-up period.[22] On the other hand, in another study to determine if baseline vitamin D level predicts the subsequent COPD exacerbation, it was observed that baseline vitamin D level had no relationship between time till the first COPD exacerbation or COPD exacerbation rates.[4] Beside this, no significant difference was observed in the re-hospitalization rate after a single parenteral high dose of vitamin D (300 000 IU) administration during hospitalization for COPD exacerbation.[23] A recent meta-analysis also demonstrated that there was not enough evidence to support the association between VDD and COPD exacerbation.[12] So, the relationship between VDD and COPD exacerbations remains controversial and needs to be illuminated.

There are limitations of this study. The study was retrospective, and there was no control group. Nutritional factors affecting the vitamin D level, sun exposure, seasonal differences could not be evaluated. A single assessment of vitamin D level may not be enough for the decision of the patient's overall vitamin D status. Also, we could not evaluate whether the patients began vitamin D supplementation or not. These limitations should be taken into consideration when evaluating the findings of this study.

There are many arguments about the relationship between vitamin D level and COPD. VDD seems to be more frequent in COPD patients than in healthy people. One of the hypothesis about why COPD patients are more prone to VDD is that these patients have decreased outdoor activity due to dyspnea, so get less exposure to sunlight which is necessary for the synthesis of vitamin D by skin. Also, frequent steroid use, malnutrition, and frequent hospitalization might be a reason for muscle loss, which further affects patients' daily activities. All of these might be the contributors to furthermore reduction of vitamin D level. Apart from these, smoking reduces active vitamin D production and vitamin D receptor expression, which all may take a role in VDD in COPD. The effect of vitamin D replacement therapy over dyspnea, quality of life, annual pulmonary function decrement and exacerbation is still controversial. Even the level of vitamin D for proper lung function is not certain. Besides many unknown, we do not even know VDD is a chicken or an egg.

In conclusion, we found that lung function was worse in COPD patients with VDD, and VDD increased with increasing severity of COPD in this study. As the vitamin D level decreased gradually, the dyspnea score increased. Exacerbation and hospitalization in patients without VDD were significantly lesser than in patients with VDD. So, as VDD takes a role in multiple aspects of COPD, vitamin D supplementation to COPD patients with VDD might decrease respiratory symptoms, improve lung functions and reduce exacerbations.

Ethics Committee Approval: This study was approved by Ethics committee of Akdeniz University, (Approval No: 12.08.2015/70).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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