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Research Article

EVALUATION OF THE RELATIONSHIP BETWEEN VITAMIN D LEVELS IN COPD PATIENTS WITH ACUTE RESPIRATORY FAILURE

***Dilek Atik*[1,*]** ***Basar Cander*[2]** ***Cesareddin Dikmetas*[2]** ***Serkan Dogan*[2]**
***İbrahim Çaltekin*[1]** ***Levent Albayrak*[1]** ***Emre Gokçen*[1]** ***Bensu Bulut*[2]**

[1] Department of Emergency Medicine, Yozgat Bozok University, Yozgat, TURKEY
[2] Department of Emergency Medicine, University of Health Sciences Kanuni Sultan Suleyman Research and Training Hospital, İstanbul, TURKEY

[*] Corresponding author; dr.dilekgok82@hotmail.com

Abstract: *Chronic obstructive pulmonary disease (COPD) can be prevented and treated condition that affects patients' quality of life, also one of the important diseases with increased mortality and morbidity due to smoking and increasing age. In our study, we aimed to evaluate the serum D vitamin level in COPD patients with acute respiratory failure and to investigate the effect of vitamin D in COPD stages. This study is a prospective cross-sectional study. The study was conducted with a total of 75 COPD patient groups and 65 control groups. Global Initiative for Chronic Obstructive Lung Disease (GOLD) score, COPD Evaluation Test (CAT) score, and Modified Medical Research Council Dyspnea Scale (mMRC) score were used in the study. All statistical data were analyzed by SPSS 20.0 for Windows. The results were evaluated in terms of p <0.05 significance level. According to the results of our study, vitamin D level in acute exacerbation was lower in patients with the acute obstructive pulmonary disease than in the control group. According to the results obtained in our study, when CAT scores, mMRC scores, vitamin D levels, and gold stages, which are the measured assessment for chronic obstructive pulmonary disease patients, are evaluated; with increasing vitamin D deficiency, patient clinics become more severe. We believe that patients diagnosed with COPD add vitamin D to their treatment protocols according to their vitamin D levels and their vital activities will increase while reducing the severity of COPD.*

Keywords: *COPD Patients; Vitamin D; GOLD staging; COPD assessment test; mMRC score*

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1. Introduction

According to the World Health Organization and TUIK (Turkish Statistical Institute) data, COPD ranks number three as the cause of death among chronic respiratory diseases [1,2]. Although Chronic Obstructive Pulmonary Disease (COPD) can be prevented and treated, it is a condition that affects an individual's quality of life and is one of the diseases with increased mortality and morbidity due to

smoking and increasing age [3-5]. Since COPD is not only fatal but also leads to disabilities, the number of people with disabilities is increasing day by day [2].

In exacerbation of COPD, unlike the stable COPD phenomenon, it is manifested by an increase in dyspnea, a decrease in daily activation, and a change in sputum amount and color. As COPD disease progresses, the number and severity of exacerbation increase [6]. Also, accompanying chronic health problems (comorbidities) affect the natural course of the disease [7]. Although it is a disease involving the lungs, it may also cause systemic effects [6].

With the development of inflammation in the alveoli as a result of exposure of harmful gases to the bronchi and bronchioles in the lungs, irreversible airflow restriction and respiratory symptoms occur [8,9]. As a result of changes in small airways that are chronically inflamed, restriction occurs during expiration. Although the severity and frequency vary clinically, patients progressively develop shortness of breath, cough, and mucus secretion [7]. Considering that smoking is an important factor in COPD, it has been stated in the literature that vitamin D may play an important role in the pathogenesis and progression of COPD [10]. As changes in the airways increase, the number and severity of COPD also increase [8].

According to GOLD criteria, COPD is diagnosed in the presence of appropriate symptoms and risk factors in case FEV1/FVC ratio is below % 70 after bronchodilator [11]. In addition to spirometric evaluation after 2011 according to the GOLD classification in COPD patients, it was suggested that patients should be evaluated together with the risk of exacerbation, mMRC scale, and COPD assessment questionnaire in the evaluation of current symptom status [11]. In cases where spirometry cannot be used continuously in patient follow-ups, it is important to use these scales in following the clinical course of the patient.

90-95% of vitamin D is a steroid-based vitamin produced in the skin and is also defined as a hormone because it acts in different regions outside of where it is produced [12]. There is a vitamin D receptor in target organs so that vitamin D can show its activity in the human body. 1.25 (OH)2D3 active metabolite shows its activity by binding to the vitamin D receptor (VDR) in target organs. The active metabolite of vitamin D hormone also regulates many genes related to cell differentiation and proliferation [13,14].

Vitamin D, the importance of which was not understood before, is thought to be a risk factor in chronic diseases through the vitamin D receptor (VDR) found in many places in the body. Today, it is known that vitamin D deficiency has effects primarily on bone, and it poses a risk for autoimmune diseases, cardiovascular system diseases, type 2 diabetes, some cancer diseases, and infectious diseases [15,16]. In the literature, vitamin D deficiency has been reported in approximately 40% of European countries [17].

Vitamin D is effective in cellular and humoral immunity [18]. Vitamin D plays an active role in mostly T cells in the immune system [19]. It activates anti-inflammatory mechanisms by activating the anti-inflammatory mechanism in Thelper 2 (Th2) cells and by inhibiting the release of IFN-γ, IL-2, IL-3, and TNF-α in T helper 1(Th1) cells and by inhibiting the activation of the proinflammatory mechanism. In vitamin D deficiency, proinflammatory mechanisms are activated from Th1 cells and they play a role in the etiopathogenesis of autoimmune chronic systemic diseases [20]. Active vitamin D also stimulates the synthesis of antimicrobial peptide-catelicide from 'natural killer' cells and epithelial cells of the respiratory tract [17, 20]. Besides, vitamin D receptors found in vitamin D monocyte and

macrophage epithelial cells also prevent infections from the respiratory tract [17]. In a study on lung diseases and vitamin D levels, it was reported that vitamin D levels had an inverse relationship with mortality [21].

In our study, it was aimed to evaluate serum D vitamin level in COPD patients with acute respiratory failure and to investigate the effect of vitamin D in COPD stages.

2. Methods

2.1. Study subjects

This study was conducted between 15.10.2019-15.12.2019 and is a prospective cross-sectional study. The study was planned in patients with acute exacerbation of COPD and volunteer healthy control group in the Training and Research Hospital Emergency Medicine Clinic, and the patients and the volunteer control group were informed about the procedures to be performed and an informed volunteer consent form was taken. Also, in the study with scoring systems, it was planned to evaluate the patients with COPD at the level of vitamin D according to their stages. The study was conducted with a total of 75 COPD patient groups and 65 control groups. Age, gender, spirometric staging, COPD evaluation questionnaire, mMRC scale, vitamin D levels, blood gas values of the patients included in the study were recorded. After explaining maneuvers on the first day of referral, the spirometric measurement was performed on the patient group. Patients who came for dyspnea not related to COPD disease, patients who did not agree to participate in the study, and those who used vitamin D preparate were not included in the study.

The patients were staged according to the GOLD guideline updated in 2021. The staging of the score is divided into 4 groups: A, B, C, D [22]. CAT scoring was done with the COPD assessment questionnaire. CAT scoring was divided into 4 groups as 1st group <10 points, 2nd group 11-21 points, 3rd group 21-30 points, 4th group 31-40 points. With the mMRC scale, 5 group staging of patients was made in terms of dyspnea. According to the clinical results of the patients, they were divided into 3 groups as discharge, hospitalization, and intensive care unit.

Ethical statements: Before the commencement of the study, the approval of the ethics committee was obtained from the Bozok University ethics committee. (Decision Date and number: 16/10/2019 and 2017-KAEK-189_201910-16_22). The study was conducted in line with the principles of the Helsinki Declaration.

2.2. Blood collection and measurement of plasma vitamin D3 level

For vitamin D measurement; Blood samples were collected in disposable, 10 ml, vacuum, anticoagulant, biochemical tubes, 5-7 ml for vitamin d measurement from patients and control groups, and centrifuged at 2500 rpm for 10 minutes, and serum was separated. Separated serums were stored at -80°C until examined. Each serum was only dissolved once on the day of the study. The measured form in the blood is 25 OH vitamin D levels. Under 20 ng/ml, 20-29 ng/ml, 30 ng/ml and higher and over 150 ng/ml were considered as deficiency, insufficiency, normal (normal value 40-60 ng/ml), and intoxication, respectively [23].

2.3. COPD clinical parameters

GOLD staging: Patients were staged as light (FEV1≥80%), moderate (50%≤ FEV1≤80%), advanced (30%≤FEV1≤50%), and very advanced (FEV1<30%) by performing spirometric staging.

CAT: The COPD assessment test was developed by Jones et al. to measure health status in COPD and to assess disease effect and severity [24].

In our country, the validity and reliability study was carried out by Yorgancıoglu et al. [25]. The test, which consists of eight questions, provides information on the rating of the disease, scoring of symptoms, and its effect on the patient's quality of life. It includes problems such as dyspnea, cough, expectoration, as well as symptoms such as fatigue and sleep problems. For each question, scoring is done between 1 and 5 (0: no symptoms, 5: serious symptoms). As a result of the scoring, it is determined that as the scores decrease, the severity of the disease decreases 26 and the health condition improves. According to the scoring, Excellent health: 0 points (minimum score), worst health: 40 points (maximum score) [24].

mMRC score: This scale was first used by Fletcher to evaluate lung diseases. The British Medical Research Council (MRC) started using this scale to monitor the natural course of COPD disease [26]. Modified Medical Research Council Dyspnea Scale (mMRC) is quantified disability attributable to breathlessness. It is a five-item scale based on a variety of physical activities that create the feeling of dyspnea. Here, patients are asked to mark the level of activity that causes dyspnea in themselves [27].

Combined assessment COPD staging: With the classification of patients as spirometric, it is recommended to determine the level of dyspnea with CAT score or Modified Medical Research Council Scale (mMRC) scores in the evaluation of symptoms [28]. The staging of the score is divided into 4 groups: A, B, C, D.

2.4. Statistical analysis

All statistical data were analyzed by SPSS 20.0 for Windows. Kolmogorov Smirnov test and skewness-kurtosis method were used to evaluate the normal distribution of all variables. In addition, the normal distribution of the data was evaluated by the histogram, one of the graphical methods. Descriptive statistics were used in the demographic examination of the patients. Within the scope of clinical research, Chi-Square (χ^2) was used to evaluate independent, categorical variables. In the study data, numerical values are expressed as mean ± standard deviation. The data obtained by the study carried out within the scope of clinical research are statistically nonparametric. For this reason, Kruskal-Wallis H test and Mann-Whitney U tests were used in statistical evaluations according to the categorical (nominal or ordinal) status of the related variables and the numerical independent group. Spearman rank correlation method was used in nonparametric data for correlations between data. The results were evaluated for a significance level of $p < 0.05$.

3. Results

78 COPD acute exacerbation patients and 65 healthy control groups participated in the study. The mean age of the patients was 70.82±10.7 years, and the mean age of the healthy control group was 72.2±7.84 years. There was no statistically significant difference between the control and patient groups included in the study in terms of age (χ^2=3.079; p=0.07). 66.7 % (n=52) of the patients in the study were male and 33.3 % (n=26) were female. 63.1% (n=41) of the control group in the study were male

and 36.9% (n=24) were female. There was no statistically significant difference in gender of the participant groups participating in the study (χ^2=4.768; p=0.06). The mean vitamin D of the patient group was 11.3±6.49 ng/ml and the mean vitamin D of the control group was 17.7±8.83 ng/ml. D vitamin level difference between the groups was found statistically significant (Z=-5.303; p≤0.001). According to the clinical results, the mean vitamin D of the patients was 11.54±6.61 ng/ml for those discharged, 9.79±4.73 ng / ml for those hospitalized, 3±0.2 ng / ml for those in the intensive care unit. According to clinical results, this difference in vitamin D levels between the groups was found statistically significant (χ^2=5.634, p<0.05) (Tab. 1).

Table 1. Demographic Characteristics Data of Participants

Demographic Characteristics - Independent Variables (IVs)	Name of Characteristics	Number	Percent (%)	Mean±SD	p
Patients Groups Gender	Female	26	33.3		
	Male	52	66.7		
	Total	78	100		
Control Groups Gender	Female	24	36.9		
	Male	41	63.1		
	Total	65	100		
Statistics Analysis					0.06
Patients Groups Age				70.82±10.7	
Control Groups Age				72.2±7.84	
Statistics Analysis					0.07
Vitamin D Level Average (ng/ml)	***Patients Groups***			11.3±6.49	
	Control Groups			17.7±8.83	
Statistics Analysis					0.001**
Clinical results of patients	Discharged With Health	47	60.2		
	Hospitalized	21	27		
	İntensive Care Unit	10	12.8		
Average vitamin D according to the clinical results of the patients(ng/ml)	Discharged With Health			11.54±6.61	
	Hospitalized			9.79±4.73	
	İntensive Care Unit			*3±0.2*	
Statistics Analysis					0.048*

*p<0.01; ** p<0.05

Table 2. Statistical results of vitamin D levels of COPD patients according to GOLD classification

GOLD classification	*Vitamin D Mean±SD(ng/ml)*	χ^2	*p*
Group 1 (mild)	16.22±6.33		
Group 2 (average)	8.7±4.05		
Group 3 (advanced stage)	8.57±4.36		
Group 4 (very advanced stage)	7.8±3.9		
Kruskal Wallis H Statistics Analysis Result		24.706	0.001*

Global Initiative for Chronic Obstructive Lung Disease =GOLD * p<0.01

According to the GOLD classification, mean vitamin D values were Group 1 (mild) 16.22±6.33 ng/ml, Group 2 (average) 8.7±4.05 ng/ml, Group 3 (advanced stage) 8.57±4.36 ng/ml, Group 4 (very advanced stage) 7.8±3.9 ng/ml. A statistically significant difference was found between groups according to the GOLD classification of vitamin D level (χ^2=24.706; p≤0.001) (Tab. 2). When the correlation between the GOLD staging of patients and vitamin D level was evaluated, a statistically negative weak correlation was found (r_s=-0.375, p≤0.001) (Tab. 6).

Table 3. Statistical results of vitamin D levels of COPD patients according to the COPD assessment test (CAT)

The COPD assessment test (CAT) Groups	***Vitamin D Mean±SD(ng/ml)***	χ^2	***p***
Group 1	9.7±9.2		
Group 2	6.79± 6.14		
Group 3	6.78±4.92		
Group 4	6.68±5.42		
Kruskal Wallis H Statistics Analysis Result		19.954	0.001*

* p<0.01

Average vitamin D values between CAT groups are shown in Tab. 3. This difference was found statistically significant in the vitamin D levels between CAT groups (χ^2=19.954; p≤0.001) (Tab. 3). When the relationship between the patients' CAT scoring and vitamin D level was evaluated, a moderately negative correlation was found (r_s=--0.667, p=0.049) (Tab. 6).

Table 4. Statistical results of vitamin D levels of COPD patients according to mMRC staging

mMRC score Groups	***Vitamin D Mean±SD(ng/ml)***	χ^2	***p***
Stage 0	11.4±9.85		
Stage 1	8.38±5.44		
Stage 2	5.89±3.74		
Stage 3	5.54±6.06		
Stage 4	4.63±4.57		
Kruskal Wallis H Statistics Analysis Result		23.746	0.001*

mMRC=Modified Medical Research Council Dyspnea Scale; *p<0.01

Table 4 shows the average vitamin D levels according to mMRC staging. This difference in vitamin D level in mMRC staging was statistically significant (χ^2=23.746,p≤0.001) (Tab. 4). When the correlation between patients' mMRC staging and vitamin D levels was evaluated, a statistically moderate negative correlation was found (r_s=--0.574, p≤0.001) (Tab. 6).

Table 5. Statistical results of vitamin D levels of COPD patients according to Combined assessment COPD staging

Combined assessment COPD staging	***Vitamin D Mean±SD(ng/ml)***	χ^2	***p***
Stage A	9.43±9.06		
Stage B	8.53±10.53		
StageC	6.99±5.98		
Stage D	6.34±4.85		
Kruskal Wallis H Statistics Analysis Result		23.571	0.001*

*p<0.05

Table 6. Correlation of Vitamin D Levels of COPD Patients According to Scoring Systems

Scoring Systems	r_s	***p***
GOLD staging	-0.375	0.001*
The COPD assessment test (CAT)	-0.667	0.049*
mMRC score	-0.574	0.001*
Combined assessment COPD staging	-0.279	0.013*

*p<0.05

According to the combined assessment of COPD staging, mean vitamin D values are shown in Tab. 5. This difference in the vitamin D level between the stages was found to be statistically significant (χ^2=23.571, p≤0.001) (Tab. 5). When the correlation between the combined stating of the patients and vitamin D level was examined, a statistically negative and weak relationship was determined (r_s=-0.279, p<0.05) (Tab. 6).

4. Discussion

According to the results of our study, low vitamin D levels were found in healthy and patient individuals. Vitamin D levels found in our study were below the normal vitamin D limits determined by Pludowski in the literature (23). This situation shows us that Turkish society cannot benefit from sunlight sufficiently. In addition, according to the results of our study, vitamin D level was lower in patients with COPD acute exacerbation compared to the control group.

Apart from its effects on bone, the effects of vitamin D on other organs have been investigated recently. It has been reported that vitamin D is an active vitamin D synthesized from T cells and epithelial cells in the action mechanism of respiratory system diseases [29]. In a previous study, they reported that the relationship between COPD and vitamin D deficiency was due to an increase in inflammation, a decrease in pulmonary functions, and a decrease in immunity [30]. In another study, they reported that vitamin D levels were low in all stages of COPD disease compared to people without COPD [31]. In a study conducted in the literature, it was reported that vitamin D affects spirometric functions, but they could not find its relationship with COPD [32]. In our study, unlike that study, vitamin D was found to be higher in patients with mild stage than advanced COPD patients in staging according to GOLD classification. When evaluated in the symptomatic stages added after 2011 in the GOLD guideline, those with high CAT scores according to the COPD assessment test (CAT) also have low vitamin D levels, and as the CAT score increases, the severity and number of exacerbation of COPD increases. Low vitamin D suggests that it affects the severity of COPD disease and the number of exacerbations. In their studies, Erdinç et al. reported that CAT scoring correlated with GOLD spirometric scoring [33]. In our study, all scoring systems are similar to the literature and show correlation with each other. It is reported in the literature that there is a correlation between lung functions and vitamin D levels in the general population [34]. In a study conducted in Belgium, it was reported that vitamin D decreased COPD exacerbation [35]. The results in our study correlate with this study. While vitamin D itself is an antioxidant, it also increases antioxidant mechanisms [36]. Therefore, we think that vitamin D alleviates the course of the disease due to its antioxidant function in diseases that develop in the inflammatory process. Some of the studies with vitamin D supplements did not provide additional benefits to individuals with COPD, but in some studies, a reduction in exacerbation has been reported in patients with severe vitamin D deficiency [37, 38, 39]. In another study, they reported to COPD patients that their quality of life increased after vitamin D supplementation, but there was no mortality and hospitalization effect [40]. In our study, unlike this study, when the clinical results are evaluated, we see that the patients' clinical course and hospitalization rates increase as the vitamin D level decreases. Although COPD disease starts at around 30s, the severity of the disease increase with the advancement of age as with the decrease in the mobility of the patients. People feel the effects of vitamin D deficiency more due to the vitamin D receptors throughout the body, which affect the muscular system, cardiovascular system, and respiratory system. Based on the results of our study, when

CAT scoring, mMRC scoring, and vitamin D levels, besides the gold staging, which is the spirometric evaluation in COPD patients, are considered; the patients' clinics become more severe as the vitamin D deficiency increases.

5. Conclusion and Recommendations

It suggests that the clinical course of these patients has been affected by the increase in the level of vitamin D in COPD patients and the increase in the severity of the disease in all 3 scorings. We think that the patients who are diagnosed with COPD add vitamin D to their treatment protocols according to their vitamin D levels, and their vital activities will increase with decreasing the severity of COPD disease.

Ethical statements: Before the commencement of the study, the approval of the ethics committee was obtained from the Bozok University ethics committee. (Decision Date and number: 16/10/2019 and 2017-KAEK-189_201910-16_22). The study was conducted in line with the principles of the Helsinki Declaration.

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