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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Relationship between chronic obstructive pulmonary disease and levels of vitamin D

Kronik obstruktif akciğer hastalığı ile vitamin D düzeyi arasındaki ilişki

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ABSTRACT

Objective: Vitamin D deficiency may be associated with pulmonary function deterioration. The aim of this study is to assess the relationship of serum vitamin D levels with pulmonary functions, disease severity and exacerbation frequency in Chronic Obstructive Pulmonary Disease (COPD) patients.

Methods: Seventy consecutive patients with COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II-IV) who presented to our outpatient clinic and thirdty controls entered to the study. Diagnosis of COPD was confirmed according to clinical findings and pulmonary function test. Serum 25-hydroxyvitamin D (25(OH)D levels were measured by immunofluorescence method. Levels <20 ng/mL defined deficiency. Associations between Vitamin D levels and sex, age, body mass index (BMI), smoking habit, comorbidities, exacerbation frequency were examined.

Results: The mean age of patients was 60.7 years. The proportion of patients in stages 2 of GOLD was 40 %, in stages 3 was 30 % and stages 4was 30 %. There was no significant difference in serum levels of 25(OH)D between COPD patients and controls. Vitamin D level was 9.3 ±6.0 ng/mL in control group and 9.7± 8.5 ng/mL in GOLD stage 2, 9.6 ± 6.2 ng/mL in stage 3 and 5.1 ±2.4 ng/mL in stage 4. In stage 4, vitamin D levels was significantly lower statistically (p=0.03). Among the COPD patients, lower FEV1 was associated with lower levels of 25(OH)D (p= 0.03). The most frequent comorbidities were hypertension (61.4%) and heart failure (27.1%). Among the COPD patients smoking associated with significantly lower levels of serum 25(OH) D (p=0.04). We find an association with exacerbation frequency in the previous 12 months and levels of 25(OH) D (p=0.02).

Conclusion: COPD severity according to GOLD stage is also associated with low levels of 25(OH)D. Serum vitamin D levels are lower in COPD patients who are current smokers. Severe vitamin D deficiency is related to more frequent disease exacerbations. These findings indicated a relationship between serum 25(OH)D concentrations and COPD which suggests optimization of serum vitamin D levels in COPD.

Key words: Pulmonary functions, Vitamin D, COPD

ÖZET

Amaç: Vitamin D eksikliği, solunum fonksiyonlarında bozulma ile ilişkili olabilir. Çalışmamızda Kronik Obstruktif Akciğer Hastalığı (KOAH) hastalarında solunum fonksiyonları, hastalığın şiddeti ve alevlenme sıklığı ile serum Vitamin D düzeyi arasındaki ilişkiyi belirlemeyi amaçladık.

Yöntemler: Polikliniğimize başvuran 70 KOAH hastası (GOLD Sınıflaması Evre II-IV) çalışmaya alındı. 30 sağlıklı gönüllü kontrol grubunu oluşturdu. Klinik bulgular ve solunum fonksiyon testine göre KOAH tanısı kondu. Serum 25-hidroksi vitamin D (25(OH)D) seviyesi immünofloresan yöntemi ile ölçüldü. 20 ng/mL altındaki değerler eksiklik olarak kabul edildi. Vitamin D düzeyi ile cinsiyet, yaş, Vücut Kitle İndeksi (VKİ), sigara içme durumu, komorbiditeler, alevlenme sıklığı arasındaki ilişki araştırıldı.

Bulgular: Hasta grubunun yaş ortalaması 60,7 yıldı. Hastaları GOLD sınıflamasına göre ayırdığımızda %40'ı Evre II, %30'u Evre III, %30'u Evre IV KOAH'tı. Hasta ve kontrol grupları arasında serum 25(OH)D düzeyi bakımından anlamlı farklılık görülmedi. Vitamin D düzeyi kontrol grubunda 9,3 ±6,0 ng/mL, Evre II KOAH'da 9,7± 8,5 ng/mL, Evre III'te 9,6 ± 6,2 ng/mL ve Evre IV'te 5,1 ±2,4 ng/mL olarak belirlendi. Evre IV te Vitamin D düzeyi düşüklüğü istatistiksel olarak anlamlıydı (p=0.03).

Hasta grubunda düşük FEV1, düşük 25(OH)D ile ilişkili bulundu (p=0.03). En sık görülen komorbidite hipertansiyon (%61,4) ve kalp yetmezliği idi (%27,1). Sigara içenlerde 25(OH)D düzeyi daha düşüktü (p=0,004). Son 12 aydaki alevlenme sıklığı ile serum 25(OH)D düzeyi düşüklüğü arasında ilişki saptandı (p=0.02).

Sonuç: GOLD evrelemesine göre KOAH şiddeti ile 25(OH)D düzeyi düşüklüğü arasında ilişki vardır. Sigara içen KOAH hastalarında 25(OH)D düzeyi daha düşüktür. Ciddi Vitamin D eksikliği alevlenme sıklığında artış ile ilişkilidir. 25(OH)D düzeyi ile KOAH arasındaki ilişki, KOAH hastalarında Vitamin D düzeyini iyileştirmek gerektiğini düşündürmektedir.

Anahtar kelimeler: Solunum fonksiyonları, KOAH, Vitamin D

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INTRODUCTION

Several extra-renal sites, including cells of the adaptive immune system, express the vitamin D receptor and the enzyme, 1-hydroxylase, which converts circulating 25(OH)D into the biologically active form 1,25(OH)2D [1]. Both the innate and adaptive immune systems have been implicated as important elements in the pathogenesis of COPD [2].

Vitamin D has been shown to affect dendritic cell maturation [3], T-cell activation and proliferation [4], Th1 T-cell development [5] and to decrease the expression of pro-inflammatory cytokines and chemokines by e. g. airway epithelial cells [6]. Thus, low local 1,25(OH) 2D levels could potentially contribute to inflammation and susceptibility to infections, [7]. Vitamin D has been shown to be an important regulator of both elements of the immune system [8]. Vitamin D also has been shown to directly affect processes involved in tissue remodelling such as fibroblast proliferation and collagen synthesis [9], and modulation of matrix metalloproteinase (MMP) levels [10]. All these data show vitamin D has an important role that may be associated with many diseases and functions in other tissues outside the bone metabolism [11].

Vitamin D deficiency is associated with increased risk of chronic diseases like cancer, autoimmune diseases, diabetes, infectious diseases, cardiovascular diseases and also pulmonary diseases [1]. Vitamin D has been shown to prevent airway inflammation and the development of experimental allergic asthma in mice [12]. It also helps the remodeling of airways and reverses steroid resistance which is important characteristics of COPD [13].

Low prenatal vitamin D levels may be risk factors for asthma prevalence and it is suggested that vitamin D deficiency could be associated with the severity of asthma [14]. Recent studies show that a substantial proportion of patients with chronic obstructive pulmonary disease have deficient vitamin D levels (<20 ng/mL) [15]. In COPD, the risk of vitamin D deficiency is higher than expected and is linked with disease severity [16]. In a study reported that vitamin D deficiency occurs in over 60% of patients with severe COPD, and is quantitatively related to disease severity [15]. Another has could demonstrated that patients with vitamin D levels below 10 ng/ml had the shortest time to first exacerbation and experienced the highest number of acute exacerbation of COPD [17]. These results suggest that Vitamin D deficiency could be associated with development, progression and exacerbation of COPD.

COPD patients may be considered as having high risk for vitamin D deficiency, because of malnutrition, reduction depends on the time they spent in sunlight at the outside, glucocorticoid-induced catabolic growth and renal dysfunction [18].

According to World Health Organization data, COPD was the fourth most common cause of death in 2000 and is expected to be the third leading cause of death in 2020 [19]. The prevalence of COPD is increasing and acute exacerbations of COPD and hospital admissions are common and strongly influence disease severity and relative healthcare costs [20]. Therefore, it is important to be able to determine the causes of increasing development of COPD, severity and exacerbations.

The present study was designed to investigate the relationship between serum vitamin D and COPD disease severity and exacerbation frequency in patients with chronic obstructive pulmonary disease (COPD).

METHODS

Written information was provided and written consent was obtained prior to inclusion. The regional ethical committee approved the study. All subjects were recruited from the same geographical area.

The study population was derived among the COPD patients presented to outpatient pulmonary clinic during the period, March 2015. They were selected among 70 consecutive COPD patients determined according to the GOLD classification [21]. Post-bronchodilator ratio of forced expiratory volume in 1 second (FEV1) to vital capacity (VC) <0.70 and FEV1 >80 % (predicted) characterized GOLD 1, 50% ≤ FEV1 <80% GOLD 2, 30% ≤ FEV1 <50 GOLD 3, 30% < FEV1, GOLD4 respectively. The patients, age over 40 years and at least one year follow-up in our clinic.

Exclusion criteria were acute exacerbation in the last month and lack of availability for data on

lung function/ exacerbations/ hospitalization the year previous to the inclusion in the study, presence of pulmonary infection, tuberculosis, pleural effusion, congestive heart failure, primary pulmonary hypertension, pulmonary emboli, restrictive airway disease, known autoimmune diseases or any active cancer in the last 5 years and conditions associated with vitamin D metabolism, absorption or taking vitamin D containing medications.

At the enrolment visit, patients underwent clinical examination recording of symptoms, smoking habits, comorbidities, medication use and exacerbations was obtained. Subjects were classified as current, former and never smoking, according to self-reported smoking history. Frequent exacerbations were defined as having ≥2 exacerbations treated with antibiotics and/or oral steroids and/or hospitalization in the last 12 months.

Body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m2), and was categorized as underweight (BMI <18.5), normal (BMI 18.5-24.99), overweight (BMI 25.0-29.99), and obese (BMI 30.0 or more) according to the current World Health Organization (WHO) classification.

Post-bronchodilator forced expiratory volume in1s (FEV) was measured for all the patients by a single expert technician in the hospital. Serum vitamin D was assessed by the measurement of 25-hydroxyvitamin D (25-OHD) by the RIA method.

Descriptive statistics for the continuous variables were presented as Mean, Standard deviation, minimum and maximum values while count and percentages for categorical variables. One way ANOVA was used to compare group means. Duncan multiple comparison test was also used to identify different group means fallow ANOVA. For determination linear relationship among variables, Pearson correlation analysis was carried out. In addition, chi-square test was performed to determine the relationship between categorical variables. Statistical significance level was considered as 5 % and SPSS (ver:13) statistical program was used for all statistical computations.

RESULTS

The characteristics of study population are presented in Table 1.

Table1. Baseline characteristics of the study sample, presented as mean ± stan for continuous and percentage for categorical variables

	COPD	Controls	p
Subjects , n	70	40	
Sex % females	52.9	53.3	
Age, years, Mean ± SD	60.7 ±9.3	57.5 ±8.9	
Smoking habits:			0.44
Never	38.6	46.7	
Ex	21.4	26.7	
Current	40.0	26.7	
BMI (kg/m^2)			0.64
<18.5	7.1	3.3	
18.5-24.9	17.1	16.7	
25-30	31.4	43.3	
>30	44.3	36.7	
FEV_1 in percent predicted*	45.4	90.3	
GOLD status			<0.001
II (FEV_1 50-80)	40		
III (FEV_1 30-50)	30		
IV (FEV_1 0-30)	30		
Exacerbations #			
<2 last 12 months	51.4		
≥2 last 12 months	48.6		
Vit D, 25(OH)D			0.491
<20 ng/ml	91.4	90	
≥20 ng/ml	8.6	10	
Comorbidity			<0.001
Hypertension	61.4	30	
Heart failure	27.1	3.3	
Diabetes	21.4	10	
Osteoporosis	10	6.6	
Obstructive sleep apnea	7.1	3.3	
Depression/anxiety	7.1	0	

BMI: Body mass index, *FEV1: Forced expiratory volume in 1 second, SD: Standard deviation
#Exacerbations requiring either hospitalization or treatment with oral antibiotics or oral steroids
**Associations were tested with t-test or Chi-square.

Seventy patients with mean age of 60.7 years and thirty controls with mean age of 57.5 years were studied. No interaction between vitamin D deficiency and gender was found in COPD patients and in controls (p=0.74 p= 0.86).

The proportion of patients in stages 2 of GOLD was 40%, in stages 3 was 30% and stages 4was 30 %. 40% of patients were current, 21.4% former and 38.6% never-smokers. Among COPD patients overall mean FEV1 in percent predicted was 45.4.

Concentrations of 25(OH) D among COPD patients and controls for different explanatory variables are shown in Table 2.

Table 2. Serum levels of 25(OH)D in ng/mL (mean ± standard deviation), for different potential explanatory variables by subject category

	COPD	Controls	p
25(OH)D ng/ml	8.3±6.7	9.3 ±6.0	
Sex			0,74
Women	8.6±7.7	9.1±5.0	
Men	8.0±5.8	9.4±6.9	
Smoking habits			0,04
Never	10.1±9.1	8.1±4.7	
Ex	9.6±4.9	10.7±7.3	
Current BMI (kg/m^2)	5.8±3.7	9.9±7.0	0.31
<18.5	5.8±4.2	12.0	
18.5-24.9	10.3±8.5	13.5±6.3	
25-30	9.5±8.3	7.8±5.2	
>30	7.0±4.7	8.8±6.5	
GOLD status			0.03
II (FEV$_1$ 50-80)	9.7±8.5		
III (FEV$_1$ 30-50)	9.6±6.2		
IV (FEV$_1$ 0-30)	5.1±2.4		
Exacerbations			0.02
<2 last 12 months	10.0±7.8		
≥2 last 12 months	6.4±4.8		

**Associations were tested with t-test and ANOVA.

Unadjusted, there was no significant difference in serum levels of 25(OH) D between COPD patients and controls. Vitamin D deficiency (<20 ng/ml) was 91.4% in COPD patients and 90% in controls. In GOLD stage group II 89.3% -group III 85.7% -group IV 100% respectively.

Vitamin D level was 9.3 ±6.0 ng/mL in control group and 9.7± 8.5 ng/mL in GOLD stage 2, 9.6 ± 6.2 ng/mL in stage 3 and 5.1 ±2.4 ng/mL in stage 4. In stage 4 vitamin D levels was significantly lower statistically (p=0,03).

Among the COPD patients, lower FEV1 was associated with lower levels of 25(OH) D (p=0.03) (Figure 1). Among the COPD patients smoking associated with significantly lower levels of serum 25(OH)D (p= 0.04) (Figure 2).

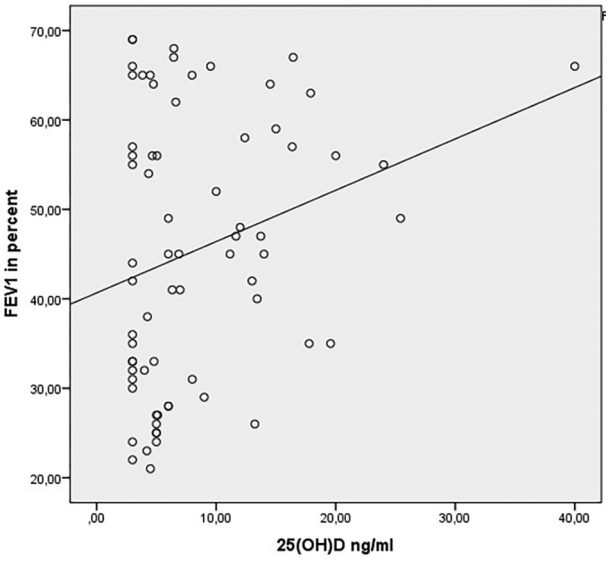

Figure 1. Relation between (correlation graphics) FEV1 (%predicted) and vitamin D levels in patient group (p=0.03).

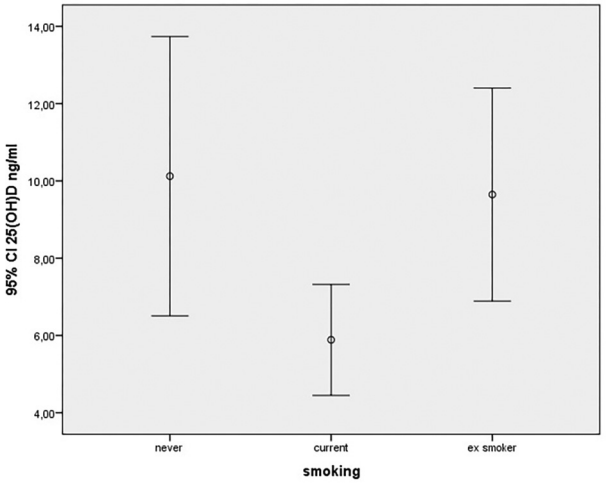

Figure 2. Vitamin D concentrations according to smoking habits in patient group (p=0.04).

The most frequent comorbidities were hypertension (61.4%) and heart failure (27.1%).Vitamin D deficiency (<20 ng/mL) was found in all comorbidities. No interaction between vitamin D deficiency and obesity was found in COPD patients (p= 0.31). In stage 4 COPD, the lower vitamin D level was statistically significant with the underweight group (p=0.035).

The patients 48.6 % were frequent exacerbators (≥2) in the previous year. We find an association with exacerbation frequency in the previous 12 months and levels of 25(OH) D (p=0.02) (Figure 3).

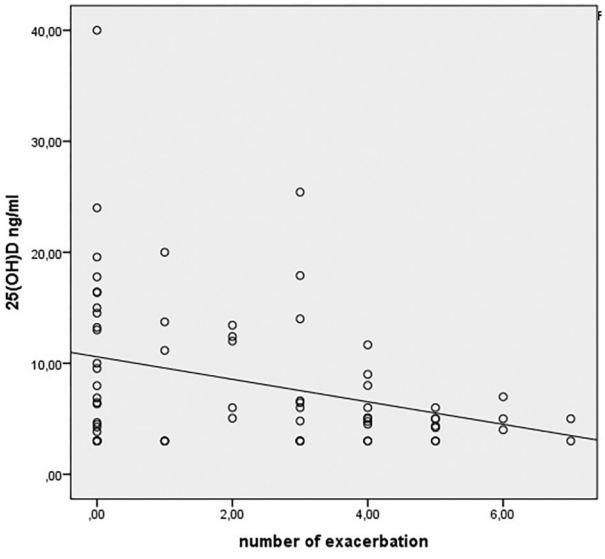

Figure3. Levels of vitamin D in COPD subjects divided according to being hospitalized the previous year (p=0.007).

DISCUSSION

Considering the general population, approximately one billion people worldwide are estimated to be sufficient vitamin D levels [22]. In studies conducted in Europe and the US in the elderly, ranging from 40% to 100% of vitamin D deficiency have been identified [22, 23]. There is not enough data in Turkey although few studies conducted on women were identified ranging from 45-75% for vitamin D deficiency [24, 25].

Many studies have been conducted to determine the normal range of 25 (OH) D for identifying the Vitamin D deficiency [26]. As a result, it was defined as 'deficient' if the 25 (OH) D level is less than 20 ng/ml, 'insufficient' if it is between 21 and 29 ng/ml and 'normal' if it is higher than 30 ng/ml [27].

The relationship between serum vitamin D and pulmonary function has been investigated in many previous studies [28, 29]. Ringbaek et al. reported that 61 patient had Vitamin D deficiency (19.6%), 82 patient had vit D insufficiency (26.4%) in 311 COPD patients. In this study, 25 (OH) D levels were positively correlated with FEV1 in COPD patients [30].

In a cross-sectional study 49 patients with mild and moderate COPD was determined, only 3 (6%) patients had sufficient vitamin D level (> 30 ng / ml), whereas 29 (59%) patients had vitamin D insufficiency (21- 29 ng / ml), 17 (35%) patients had deficiency (<20 ng / ml) [31]. In a study conducted in Norway Vitamin D deficiency was found 34% of controls, 20% of with Stage 2.43% of stage 3 and 55 % of stage 4 patients [32].

In our study, Vitamin D deficiency (<20 ng/ml) was 91.4% in COPD patients and 90% in controls. In the patients with GOLD stage II 89.3% -III 85.7% -IV 100% respectively. Compared with other studies, vitamin D levels were much lower in our study.

There are several potential explanations for the increased risk for vitamin D deficiency in COPD patients. The patients with COPD are liable to vitamin D deficiency due to lower duration of outdoor activities and inadequate sunlight exposure. COPD patients may have accelerated skin ageing due to smoking, renal dysfunction, reducing the consumption of milk and milk products, less fat tissue due to wasting and treatment with glucocorticoids, all factors that can affect vitamin D synthesis, storage or catabolism [1]. Long-term oxygen therapy is a predisposition factor of vitamin D deficiency [33].

In the elderly and healthy subjects, there was a relationship between serum 25-OHD levels and FEV1 value [34, 35]. Among COPD patients overall mean FEV1 in percent predicted was 45.4 and lower FEV1 was associated with lower levels of 25(OH) D.

In patients with more severe COPD, vitamin D deficiency is more prevalent and serum 25-OHD concentrations are lower. Janssens et al. reported that if the GOLD stage increases the average vita-

min D levels have also been significantly decreased [15].

Low levels of serum vitamin D may lead to pulmonary function test deterioration and peak exacerbation of COPD, winter and early autumn have been attributed to low concentration of serum 25(OH)D. Vitamin D was deliberately assessed in the winter season, when levels are supposed to be lowest [36]. The lowest winter vitamin D values may contribute to the marked impact of winter season on both frequency and outcomes of COPD exacerbations [37]. Performed on 198 patients with COPD in the Lung Health Study III study, seasonal changes were determined as mean 13.4 ng / ml [28].

It is important measuring vitamin D levels in patients and control groups to eliminate seasonal effects at the same time. We looked at vitamin D levels in the same month in patients and the control group. The lower values in patient and control groups may be explained the assessment in March after winter.

Lange et al reported that, the vitamin D level was lower in smokers with COPD patients and has been observed annually over the loss of FEV1 [38]. In our study, among the COPD patients, smoking associated with significantly lower levels of serum 25(OH) D (p= 0.04).

Today, except for smoking cessation therapy, there is a need for new treatment strategies in effective protecting lung function. In several studies, it has been found that vitamin D to have anti-inflammatory effects and to be regulated by enzymes such as matrix metalloproteinases associated with smoking. Vitamin D is also serving as both anti-oxidant and increasing the production of anti-oxidants. Also vitamin D could be effective on oxidative stress caused by smoking [38, 39].

Vitamin D deficiency has been associated with insulin resistance, hypertension, vascular calcification and left ventricular hypertrophy [40, 41]. In our study, COPD patients with Vitamin D deficiency had HT, heart failure, diabetes, osteoporosis, OSAS and anxiety.

Obesity has in previous studies been a significant predictor of low levels of vitamin D in both COPD patients and subjects without COPD [15, 42]. Vitamin D deficiency has been shown to impair insulin synthesis and secretion in human and animal models of diabetes, suggesting a role in the development of type 2 diabetes, which is one of the common causes of obesity and abdominal obesity [43, 44]. But in our study, no interaction between vitamin D deficiency and obesity was found in COPD patients (p=0.31). In stage 4 COPD, the lower vitamin D level was statistically significant with the underweight group (p= 0.035).

Skeletal muscle weakness is one of the most fundamental systemic effects of COPD and an important determinant of exercise capacity [45]. In severe COPD groups after dissolution in muscle have increased risk of hospital readmission, exacerbations and mechanical ventilation. Also Vitamin D deficiency is an independent risk for mortality of COPD [46].

Severe deficiency was associated with frequent exacerbations and hospitalization. The lowest winter vitamin D values may contribute to the marked impact of winter season on both frequency and outcomes of COPD exacerbations [36, 37]. Several studies demonstrate that vitamin D plays a role in susceptibility to airway infections [47].One explanation for this is the already mentioned role of vitamin D in the innate immune response, including its ability to induce the production of antimicrobial peptides [48]. In the current study, we find an association with exacerbation frequency in the previous 12 months and levels of 25(OH) D.

In a study conducted in Belgium, there is evidence that vitamin D supplementation could reduce moderate and severe exacerbations in patients with COPD. High dose vitamin D supplementation has been found to decrease acute exacerbations, but only in patients with severe deficiency [49]. The effect of vitamin D supplementation in COPD is still debated.

In conclusion, the results of this study indicate a relationship between serum 25(OH) D levels and COPD. COPD patients had an increased risk for having vitamin D deficiency. 25(OH) D concentration is statistically significantly lower in COPD patients who are current smokers and who are stage 4 according to GOLD. Severe deficiency is associated with higher probability having frequent exacerbations and hospitalization. The prevention of exacer-

bations is a major treatment goal of COPD and the benefit of vitamin D supplementation particularly during the winter season, is an intervention that warrants further assessment. Future longitudinal studies are warranted to assess the predictive effect of levels of vitamin D on decline in lung function, exacerbation frequency, and changes in body composition in patients with COPD.

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